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From the Pediatric Clinic and the Department of Clinical Biochemistry, Karolinska Sjukhuset, Stockholm, Sweden

Infants of Diabetic Mothers

II. Studies on the Electrolyte Metabolism and the Effects of Starvation during the First Days of Life

by ROLF ZETTERSTRÖM and BERTIL ÅBERG

The perinatal mortality rate is considerably greater among infants of diabetic mothers than among infants with uncomplicated pregnancies (WHITE & HUNT, 1943, MILLER, HURWITZ & KUDER, 1944, and others). The cause of this lessened viability is not completely known, but factors such as an intrauterine hypoxia (BERGLUND & ZETTERSTRÖM, 1954) and an abnormal hormonal balance in the mother (WHITE & HUNT, 1943) might interfere with the infant's viability. Generalized edema is a striking symptom among the newborn infants of diabetic mothers, and this edema probably causes other characteristic symptoms. Thus, respiratory insufficiency might be caused by pulmonary edema, and signs of cerebral damage might be caused by cerebral edema. The tendency toward pulmonary hyaline membranes (FARBER & WILSON, 1932) in newborn infants of diabetic mothers (GELLIS, 1953) and in prematurely born infants (MILLER & HAMILTON, 1949) might be due partly to the generalized edema of the respiratory organs, or might be caused by the same factors as those causing the edema. The generalized edema, as well as the considerable risk of circulatory and respiratory failure due to it, has led us to let the infants of diabetic mothers thirst and fast during the period of edema, i.e. the first two or three days of life. The treatment has thus been the same as that recommended by CLIFFORD (1947) for edematous prematurely born infants.

This communication deals with various metabolic investigations during the fasting period and following administration of food and water. Variations in blood sugar as well as in the non-protein nitrogen level (NPN) have been investigated. Due to the general edema of the infants studied, it was also of interest to study the electrolyte balance in the neonatal period. The electrolyte balance was also considered to be of special interest because of the demonstration of endocrine abnormalities at autopsy in infants of diabetic mothers (SMYTH & OLNEY, 1938, OKKELS & BRANDSTRUP, 1938,

and POTTER, SECKEL & STRYKER, 1941), as well as in animal experiments (HULTQUIST, 1950). Quite recently BJÖRKLUND (1953) has found that electrocardiographic changes of the same type as in hypopotassemia occur among these infants.

Methods

Urine was collected quantitatively during the time of electrolyte balance studies. The loss of electrolytes in the faeces and sweat have not been taken into account. Thus, the figures for the loss of electrolytes, which were calculated from the data obtained, are too low. However, the loss of potassium at least is very low in the faeces (HANSEN & SMITH, 1953) and in sweat (DI SANT'AGNESE, DARLING, PERERA & SHEA, 1953), compared with the loss in the urine. When the infants were fed, pooled human breast-milk was given which was analysed for sodium, potassium, chloride and nitrogen. The same pooled milk was used in all investigations performed.

Sodium and potassium in blood serum and urine were determined with a Beckman flame-photometer. Chlorides in blood serum and urine were electrometrically titrated (cit. MÜLLER, 1921). The carbon dioxide combining power of the blood was determined according to VAN SLYKE & CULLEN (cit. TODD & SANFORD, 1944). NPN was estimated after Nesslerization and the blood sugar was determined as total reducing substances with the HAGEDORN & JENSEN method (cit. HAWK, OSER & SUMMERSON, 1947). Urinary nitrogen was estimated with a modified Kjeldahl method.

Material

Ten consecutive surviving infants of diabetic mothers were studied. The infants were admitted to the Paediatric Clinic from the maternity hospital immediately after birth. The electrolyte balance studies were started as soon as the infants arrived at the clinic.

The electrolyte balance was studied for at least one week in five infants of diabetic mothers and in one infant suffering from asphyxia neonatorum. For technical reasons only male infants were used during these studies. The main clinical data are given in Table 1. All cases except Case 5 showed symptoms characteristic of newborn infants of diabetic mothers. Case 5, who was a twin, had the best vitality, although the birth weight was only 1760 grams.

Results

The fasting blood sugar values on admission and on the mornings of the following days are given in Table 2. It is evident that although the children were fasted, there was a tendency for the blood sugar level to increase. The mean values given in the table seem to be higher than those reported in normal newborns during the first week of life (NORVAL, KENNEDY & BARKSON, 1949). The differences are, however, not statistically significant. The infants, whose values are given in Table 2, had fasted and thirsted for three days except in a few infants who did not get any food or drink during two days. The results are in agreement with those recently reported by PEDER-

TABLE 1

Clinical data of the cases who have been submitted to electrolyte balance studies.

Case no.	Duration of mother's diabetes. Years	Fetal age, Weeks	Obstetric history	Birth weight, g	Time of withholding fluid and food, Hours
1	18	35	1 stillbirth, Caesarean section	4080	84
2	27	35	3 stillbirths, Caesarean section	2980	48
3	1/2	35	Caesarean section	3960	72
4	7	36	Caesarean section	2940	84
5	2	35	Twin. Otherwise normal	1760	48
Control	—	40	No abnormalities	4480	48

Case no.	Weight loss, per cent	Edema at birth	Onset of respiration	Later asphyxial attacks	ECG findings
1	20	+ + + +	slow	several severe during first 2 days	on 6th day prolonged Q-T index
2	18	+ + +	slow	several severe during first 2 days	low T-waves first 2 days
3	16	+ + +	prompt	none	pathological between 2nd and 4th days
4	15	+ +	prompt	mild first day	no abnormalities
5	10	+	prompt	none	no abnormalities
Control	14	+ + +	prompt	several mild first 4 days	no abnormalities

SEN, BOJSEN-MÖLLER & POULSEN (1954) and KOMROWER (1954). Thus, there is no tendency to pathological hypoglycemia in infants of diabetic mothers. From Table 2 it is also evident that the non-protein nitrogen does not reach abnormal values, although no food or drink was allowed.

TABLE 2

Blood sugar and non-protein nitrogen level in the infants of diabetic mothers studied.

Day of life	Blood sugar			Non-protein nitrogen		
	Average mg/100 ml	Range	No. of determinations	Average mg/100 ml	Range	No. of determinations
1	62	46–100	10	50	42–62	5
2	74	48–116	9	59	50–67	5
3	85	61–106	10	57	50–64	6
4	84	61–114	8	61	52–75	5
5	98	72–160	8	56	49–63	5

The neonatal fall in birth weight is given in Table 3. The fall, calculated as percentage, is greater than that seen in normal infants during the first days of life. The mean total reduction in weight was 15.2 per cent, i.e. twice as much as found in normal infants. The reduction in weight is of the same order of magnitude as that seen in edematous premature infants (SMITH, YUDKIN, YOUNG & MINKOWSKI, 1949), and probably due more to loss of edema fluid than lack of food and water. Hemoglobin concentrations were checked regularly during the fasting period. In none of the cases were there any signs of hemoconcentration.

In some cases, the serum protein concentration was estimated. No real hypoproteinemia occurred during the fasting period. The serum protein concentration varied between 4.7 and 5.4 g per 100 ml, which is slightly less then the figure reported for normal infants during the neonatal period.

TABLE 3

Loss of weight in the perinatal period in 10 cases of infants of diabetic mothers. No fluid was given during the period of observation.

Day of life	Percentage of birth weight		No. of observations
	Average	Range	
1	4.0	1.0– 5.8	10
2	9.7	6.2–11 5	10
3	12.5	12 –14	6
Total weight loss	15.2	10 –20	10

TABLE 4

Electrolytes in the blood serum (mM per liter).

Case no.	Time (days)	Sodium	Potassium	Chloride	Carbon dioxide combining power
1	1	142	5.2	107	20
	5	147	4.8	115	17
2	1	148	5.8	102	23
	5	144	5.1	110	18
3	2	154	5.8	101	
	6	160	4.7	114	
6	1	145	5.9	97	22
	4	140	5.2	106	20
11	0	151	6.2	104	24
	4	157	5.2	107	21
	8			112	

i.e. 5.6 g per 100 ml (SMITH, 1951). Our figures coincide with those found in prematures (NORTON, KUNZ & PRATT, 1952). Paper electrophoresis was made on a serum sample from Case 1 on the 8th day of life. The β-globulin fraction was fairly high (0.94 g per 100 ml) and the γ-globulin fraction fairly low (0.65 g per 100 ml). The other fractions were essentially normal. These electrophoretic values agree with those found in prematures (NORTON *et al.*, 1952).

The electrolyte balance of infants of diabetic mothers during the first days of life is given in Table 4. All values during the first and second day of life are within normal limits (cf. GRAHAM, WILSON, TSAO, BAUMANN & BROWN, 1951, and STRANGERS, MAAS, RATTINGHUIS & FEHMERS, 1954). In no case were there any signs of hypopotassemia. The chloride level and, in many instances, the concentration of sodium, showed a tendency to increase. This might give rise to a tendency towards hyperchloremic acidosis not seen in normal infants (GRAHAM *et al.*, 1951) but in prematures (REARDON, GRAHAM, WILSON, BAUMANN, TSAO & MURAYAMA, 1950).

Fig. 1 shows the cumulative electrolyte balance in a grossly edematous infant of a diabetic mother (Case 1 in Table 1). As in most electrolyte balance experiments, the calculations have been performed on analyses of the food and the urine. The figure shows that the excretion was low during the first day of life but increased during the second day. The excretion of

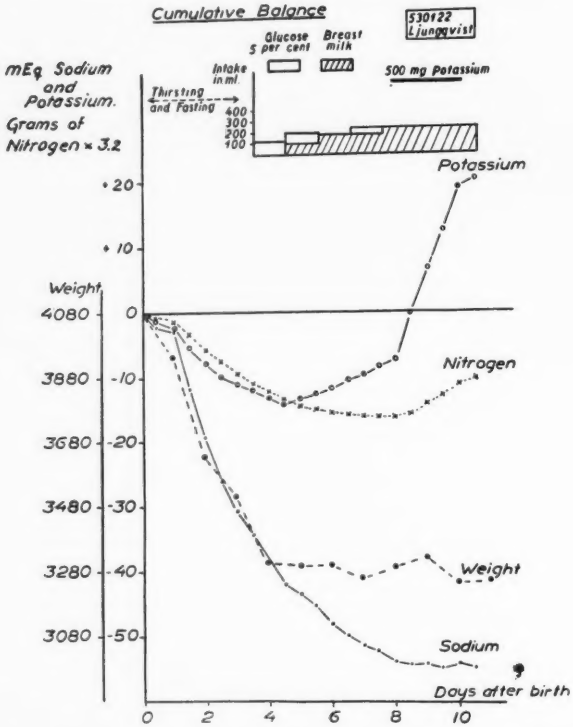

Fig. 1. Cumulative balance of electrolytes and nitrogen in a newborn infant of a diabetic mother (Case 1). The large retention of potassium after administration of this ion is clearly demonstrated. Potassium is retained when there still is cumulative loss of nitrogen. Due to the enormous edema at birth there is a very pronounced loss of sodium.

potassium was low during the thirsting and fasting period but as soon as the infant was fed with human milk, potassium was retained. The balance turned positive in a very short time if the total amount of potassium at birth was taken into consideration. The potassium balance for this case was about the same as for prematures (SMITH *et al.*, 1949). During the whole period of thirsting and fasting, sodium was lost in the urine and, in contrast to potassium, the sodium balance was negative even when human milk was given. Totally, during the $8\,^1/_2$ days with a negative sodium balance, 54.3 mEqv were lost. During the additional 2 days the loss of sodium was the same as the intake and there was thus a state of equilibrium, as there was no significant change in weight during these days. The great loss of sodium may chiefly be due to the disappearance of the edema. It is evident from Fig. 1 that the administration of 120 grams of 5 per cent

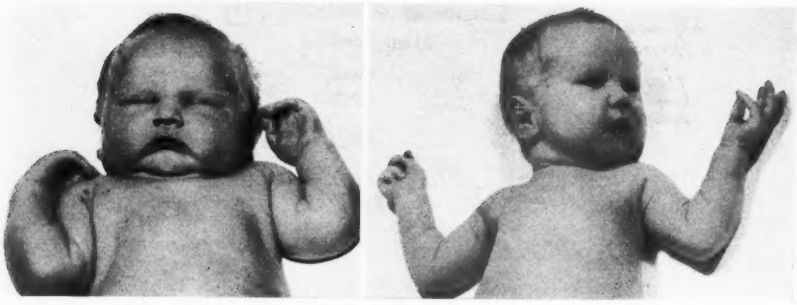

Fig. 2. Photographs of Case 1 at birth and after disappearance of the edema. The figure shows the enormous generalized edema at birth in this case.

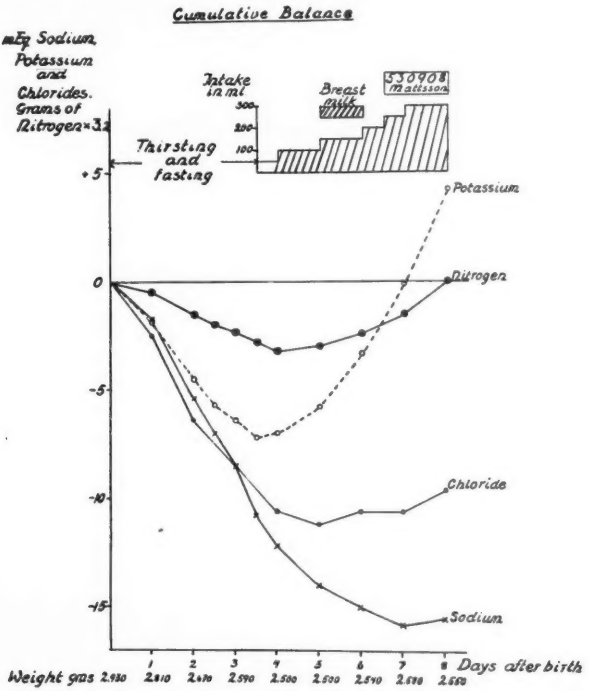

Fig. 3. Cumulative balance of electrolytes and nitrogen in Case 4 (infant of a diabetic mother). The patterns are essentially the same as those demonstrated in Fig. 1. It is clearly seen that there is a continued loss of sodium despite a retention of chloride. In this case the edema was less, hence the loss of sodium was not as great as in Case 1.

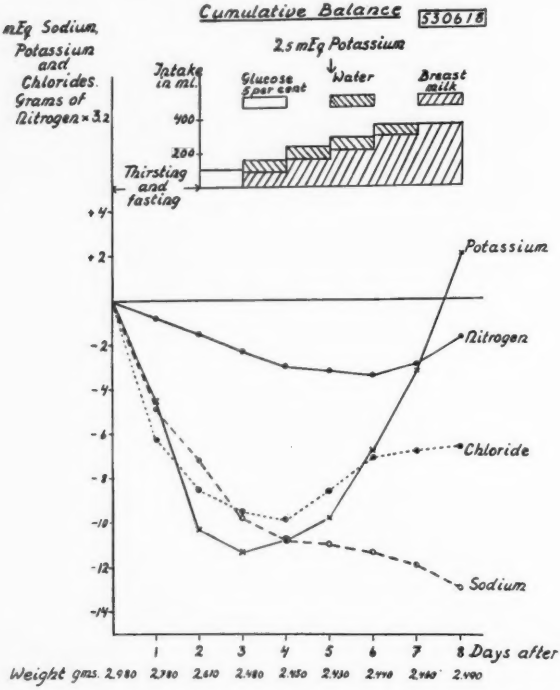

Fig. 4. Cumulative balance of electrolytes and nitrogen in a newborn infant of a diabetic mother (Case 2). As was also shown in Fig. 3 there is in this case a retention of chloride despite continued loss of sodium.

glucose solution for one day did not affect the balance of potassium and sodium, as the excretion of these ions is the same during this period as during that of complete thirst. Although 17.6 mEqv of potassium were administered during the 9th and 10th days of life (i.e. potassium in milk and extra potassium chloride), only 3.6 mEqv were found in the urine. When this value is compared with the loss of 5.9 mEqv during the 2nd day of life when no potassium was administered, it is evident, that the infant had aquired the ability to retain potassium. Fig. 2 is a photograph of the infant before and after the loss of the generalized edema.

Fig. 3 shows the cumulative electrolyte balance in another infant of a diabetic mother (Case 4, Table 1). This child was also edematous but not to the same degree as the aforementioned case. Potassium was lost, in this case also, during the period of thirsting and fasting but the loss was not as great. As soon as human milk was given, potassium was retained and in a very short time the infant had retained enough to be in positive balance

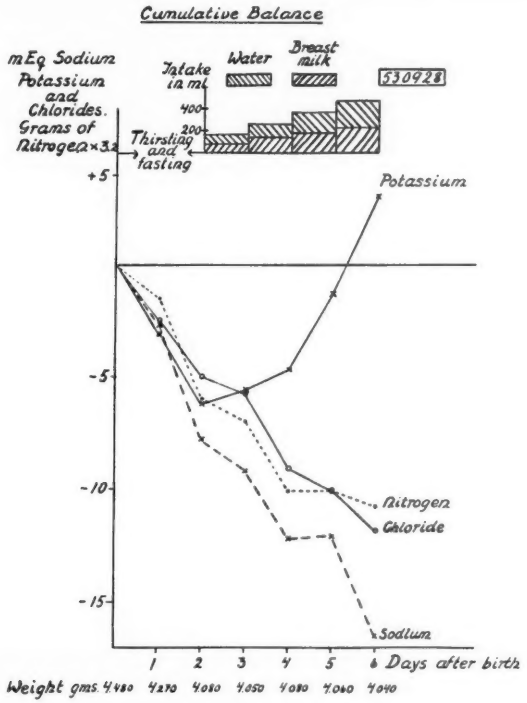

Fig. 5. Cumulative balance of electrolytes and nitrogen in a moderate edematous newborn infant with neonatal asphyxia. In this case also there is a rapid retention of potassium after administration of human milk. Due to the presence of edema at birth there is a marked loss of sodium. In this case, however, sodium and chloride are lost in about the same proportions as they occur in extracellular fluid. This finding indicates that the excess sodium present at birth in this case is exclusively extracellular.

compared with the state at birth if the loss of potassium in the meconium, faeces and sweat is disregarded. In this case, the excretion of potassium in the urine was 2.7 mEqv during the 2nd day and only 0.96 mEqv during the 9th. Thus, the excretion was also in this case considerably less when potassium was administered (in the milk) than when nothing was given. The sodium balance is in agreement with that of Case 1. Although sodium was administered in the milk, there was a continued loss of sodium. At no time, however, was the loss of the same magnitude as that in the first case, probably because there was less edema. The balance of chloride was negative as long as the sodium and potassium balance was negative. However, as soon as potassium was retained the intake and output of chloride were

TABLE 5

Average daily urinary output of sodium, potassium, chloride and nitrogen during the period of thirsting and fasting.

Case no.	Edema	Sodium mEqv/24 hrs	Potassium mEqv/24 hrs	Chloride mEqv/24 hrs	Nitrogen mg/24 hrs
1	+ + + +	2.77	0.98	—	258
2	+ + +	1.12	1.15	1.10	81
3	+ + +	1.60	0.80	1.40	132
4	+ +	1.05	0.70	0.96	—
5	+	0.65	0.62	0.50	110
Control case	+ +	0.84	0.70	0.65	200

in equilibrium. The principles of the cumulative balance of potassium, sodium and nitrogen seem to be the same in Fig. 1 and Fig. 3. The quantitative differences are probably due to different degrees of edema.

Fig. 4 shows the cumulative electrolyte balance of Case 2 in Table 1, who also was an infant of a diabetic mother. The course is the same in this case as in the two aforementioned ones. More sodium than chloride is lost. Between the 4th and 8th days of life, when there was a retention of chloride, the infant continued to lose sodium.

Fig. 5 shows the electrolyte balance in a moderately edematous full-term infant with perinatal asphyxia. Due to the fact that the balance was studied for only 6 days, the maximal loss of sodium was not reached during the time of observation. There was a relatively greater loss of chloride than of sodium. However, the curves for sodium and chloride, respectively, run parallel.

Tab. 5 gives the average daily urinary output of sodium, potassium, chloride and nitrogen during the period of thirsting and fasting in the infants whose cumulative balance was studied. The daily output of sodium seems to be correlated with the amount of edema fluid at birth. In the case with a large amount of edema the loss of sodium was considerable. In less edematous cases it was lower. The loss of chloride follows partly the same pattern as that of sodium. Considering the fairly large loss of weight during the neonatal period, the loss of potassium is fairly small. It was found to be between 0.62 and 1.15 mEqv per day per kg body weight. This value is considerably less than that observed in adults while fasting (GAMBLE, ROSS & TISDALL, 1923). Our results show no correlation between the amount of

edema fluid and the loss of potassium. There were considerable variations in the urinary output of nitrogen. Neither was there any correlation between the loss of nitrogen and the output of any electrolytes studied.

Discussion

The electrolyte balance in premature infants during the first days of life during thirsting and fasting has been studied by SMITH *et al.* (1949). Infants born at term have been studied by HANSEN & SMITH (1953). It has been demonstrated that in edematous prematurely born infants, there was an excess of sodium and chloride at birth, but this was corrected during the first days of life. Potassium was retained when this ion was administered and this was assumed to be a sign of a relative deficit of potassium at birth. In prematures who were edematous, considerable quantities of nitrogen were excreted during periods of fasting and this was also the case when food was given. Thus, there seemed to occur a very marked protein catabolism in such cases. There was a certain correlation between the amount of edema fluid and the protein catabolism. A high concentration of urea in the blood was also assumed to be a sign of a high rate of protein catabolism.

Our results in infants of diabetic mothers agree partly with those found by SMITH *et al.* (1949) in prematures, and partly with those found by HANSEN & SMITH (1953) in full-term infants. As has been observed in prematures by SMITH *et al.* (l.c.) the relative output of potassium was in all cases except one (Case 1) larger than that of nitrogen, calculated as if an intracellular destruction gives 3.2 mEqv of potassium per gram nitrogen (DARROW, 1945). This phenomenon, however, is by no means specific for the neonatal period, but is seen in all states of dehydration (GAMBLE, 1947). In all our cases potassium has been retained in such amounts that the total amount was fairly soon larger than that at birth (in Case 1 about 20 mEqv). This retention of potassium started in some cases although the daily nitrogen balance was still negative. This differs from the results obtained in infantile diarrhoea (GAMBLE, 1951). In such cases, potassium is only retained when the nitrogen balance is positive. The rapid retention of potassium in our material was not only seen in infants of diabetic mothers but also in the control case (asphyxia neonatorum). Such a rapid retention is also seen in prematures (SMITH *et al.*, 1949), and might be taken as a sign of potassium deficit at birth. However, this "deficit" seems to be connected more with the neonatal edema than with the mother's diabetes and cannot thus be an electrolyte shift caused by any special disease in the mother.

In many of our cases, the cumulative loss of chloride lessened or turned into a positive balance when potassium was administered although sodium

was still lost. It thus seems probable that in those cases there was a surplus of sodium intracellularly which was replaced by potassium when this ion was administered. The intracellular sodium was then excreted in the urine and the infant's total content of sodium was decreased without a corresponding decrease in chloride. In our control case, as in the cases studied by SMITH *et al.* (1949), the cumulative chloride balance followed that of sodium. A continued loss of sodium also gave a loss of chloride, and this latter ion was only retained when there was a retention of sodium. This might be taken as a sign of a greater amount of intracellular sodium in infants of diabetic mothers than in other infants studied. Should this be the case, these infants ought to retain more potassium than other infants when that ion is administered, so as to exchange the intracellular sodium for potassium. No such conclusions can be drawn from our studies, as the potassium balance was studied long enough in one case only (Case 1), and in that case chloride determinations were unfortunately not performed. However, in Case 1, 20 mEqv of potassium were retained although the weight decreased by 20 per cent. The great loss of sodium in these infants seems thus to be due not only to the extracellular edema but also to the fact that intracellular sodium is exchanged for potassium. The mechanism should consequently be the same as that observed in infantile diarrhea treated with saline (DARROW, PRATT, FLETT, GAMBLE & WIESE, 1949).

Our studies give no clue as to the cause of the general edema seen in infants of diabetic mothers. The increased intracellular sodium, however, seems to support the theory that the electrolyte balance is deranged during the fetal life of these infants. The abnormal retention of sodium might cause secondary edema. Some infants of diabetic mothers show electrocardiographic changes similar to those seen in hypopotassemia (BJÖRKLUND, 1953). BJÖRKLUND (1954) has found that the urinary excretion of 11-desoxycorticoids is higher in infants of diabetic mothers than in normal newborns. However, during the first week of life, the urinary excretion becomes normal. From these results the hypothesis was advanced that the edema might be caused by pathological adrenal cortical function. However, KLEIN, FORTUNATO & PAPADATOS (1954) have shown that there is an increased serum level of free corticoids in infants with hemolytic anemia of the newborn. Thus, there are signs of adrenal cortical hyperfunction in other diseases of newborns associated with edema. There are, however, many results which favour the theory that the fetal electrolyte balance is deranged in infants of diabetic mothers, and this derangement might, at least partly, be explained by a deranged adrenal cortical function in the mother and/or the fetus. Our results have shown that the cumulative electrolyte balance is immediately corrected after birth; therefore the adrenal cortical function

corresponds to that in normal newborns. The large surplus of sodium is rapidly excreted and there is, as well, a considerable capacity to retain potassium. This seems to correspond with the results found in premature infants, but the infants of diabetic mothers lose smaller amounts of potassium during thirsting and fasting than premature infants with edema. It is impossible to reach any conclusions as to whether an intrauterine hypoxia can be of importance for the formation of the edema of infants of diabetic mothers. Di Pasquale & Schiller (1952) have shown that in rats the critical hypoxemia value which affects the capillary permeability is 2.6 to 5.5 vol. per cent oxygen, a value which does not seem to be impossible in the fetus of a diabetic mother.

During the first days of life, several of the infants of diabetic mothers have attacks of cyanosis. Such attacks generally occur when food is administered or after vomiting. The most rational therapy thus seems to be complete thirsting and fasting during the critical period. Another reason for such a therapy is the general edema seen in such infants, which means that no water-retaining electrolytes ought to be administered. It has earlier been shown by Pedersen, Bojsen-Möller & Poulsen (1954) that there is no risk of hypoglycemia in children of diabetic mothers who are kept fasting for 24 hours. The results shown in this paper demonstrate that there is no such risk, even if the period of fasting is extended over more than 3 days. The potassium deficit which exists at birth, and the abnormal retention of sodium, make it clear that administration of extra amounts of potassium by mouth is indicated so as to hasten a positive cumulative potassium balance and accelerate the excretion of sodium (the Bunge effect, cf. Gamble, 1951).

Summary

Newborn infants of diabetic mothers have been kept thirsting and fasting during the first 2 or 3 days of life, i.e. as long as they have had generalized edema. During this period of starvation there was no tendency to pathological hypoglycemia; the blood sugar levels found in these cases were higher than that of normal newborns.

During the period of starvation and following the administration of food and water the cumulative electrolyte balance was studied in some of the cases. When no electrolytes were given there was a continued loss of sodium, potassium and chloride, the loss of sodium being much greater than that of potassium. In grossly edematous cases the sodium loss was very marked. There was no correlation between the degree of edema and loss of potassium. As soon as electrolytes were administered there was a marked retention of potassium and very rapidly the infants had retained more potassium than was present at birth. During the initial period of potassium retention there was a continued loss of sodium. Furthermore, the amount of sodium lost was higher than of chloride in relation to the composition of extracellular fluid, a finding

indicating that in infants of diabetic mothers there are at birth great amounts of sodium intracellularly.

The serum electrolyte values were within normal ranges during the first two days of life. Following the period of thirsting and fasting there was in all cases studied a slight to moderate hyperchloremic acidosis. There were no signs of hypokaliemia.

The mechanisms of the electrolyte derangement are discussed. The results have also been discussed with regard to the treatment of newborn infants of diabetic mothers.

Les enfants nés de mère diabétique. II. Etude sur la balance des électrolytes, et des effets de la diète au cours des premiers jours.

Des nouveaux-nés de mère diabétique ont été soumis à une diète complète pendant les deux à trois premiers jours, c'est à dire pendant le temps où ils présentaient un œdème généralisé. Au cours de cette période, on n'a observé aucune tendance à l'hypoglycémie, et le taux de la glycémie était même supérieur à celui de nouveaux-nés normaux. La balance des électrolytes a été étudiée dans quelques cas au cours de la période de diète, et selon l'administration d'eau et d'alimentation. En l'absence d'apport d'électrolytes, on notait une perte continue de Sodium, de Potassium, et de Chlorures, la perte de Sodium étant bien supérieure à celle du Potassium. Dans les cas, où existaient d'importants œdèmes, les pertes de Sodium étaient nettement plus importantes. Il n'y a pas de rapport entre l'importance des œdèmes et la déperdition potassique. Après l'administration d'électrolytes, on notait une importante rétention potassique, et la Kaliémie dépassait rapidement celle de la naissance. Au début de la période de rétention potassique, la perte de Sodium se poursuivait. En outre, la quantité des pertes sodiques, était supérieure à celle des Chlorures (par comparaison avec la composition des liquides extra-cellulaires), ce qui indiquait que les enfants nés de mère diabétique, possédaient à la naissance de grandes quantités de Sodium intracellulaire. Les taux d'électrolytes au cours des deux premiers jours, se situaient dans des limites normales. Dans tous les cas, on observait à la suite de la période de diète complète, une acidose hyperchlorée discrète ou modérée. Il n'y avait pas de signes d'hyperkaliémie. Les auteurs étudient les causes du trouble dans le métabolisme des électrolytes, et interprètent leurs résultats, notamment dans le traitement des enfants nés de mère diabétique.

Kinder diabetischer Mütter. II. Untersuchungen des Elektrolytstoffwechsels und die Wirkungen des Hungerns in den ersten Lebenstagen.

Neugeborene von diabetischen Müttern haben in den ersten 2 oder 3 Lebenstagen gedurstet und gehungert, d. h. so lange sie ein generalisiertes Ödem haben. In dieser Zeit absoluten Hungerns besteht keine Tendenz zur pathologischen Hypoglykämie; der Blutzuckergehalt war in diesen Fällen höher als bei normalen Neugeborenen. Während dieser Hungerperiode und der Administration von Nahrung und Wasser folgend, wurde die Elektrolytbalanz bei einigen Fällen studiert. Wenn man keine Elektrolyte gab, kam es zu einem Verlust an Natrium, Kalium und Chloriden, wobei der Natriumverlust wesentlich höher als der Kaliumverlust war. In Fällen mit ausgesprochenem Ödem war der Natriumverlust sehr ausgesprochen. Es bestand keine Beziehung zwischen der Schwere des Ödems und dem Kaliumverlust. Sobald man Elektrolyte gab, kam es zu einer bedeutenden Kaliumretention und sehr schnell hatten die Kinder einen höheren Kaliumspiegel als bei der Geburt. Im Beginn der

Kaliumretention hatten man einen kontinuierlichen Natriumverlust. Weiterhin war die Menge des Natriumverlustes grösser als die der Chloride in Beziehung zur Zusammensetzung der extrazellulären Flüssigkeit, ein Befund, der anzeigt, dass Kinder von diabetischen Müttern bei der Geburt über grosse Mengen von intrazellulärem Natrium verfügen. Die Werte der Serumelektrolyte waren in den ersten Lebenstagen innerhalb der Norm. Bei allen Fällen fand man nach der Durst- und Hungerperiode eine mässige hyperchlorämische Azidose. Es bestanden keine Zeichen einer Hypokalämie. Es werden die ursächlichen Faktoren der Störung der Elektrolytenbalanz diskutiert. Die Ergebnisse werden auch in Hinblick auf die Behandlung von Kindern diabetischer Mütter erörtert.

Niños de madres diabéticas. II. Estudios del metabolismo de los electrolitos y los efectos del hambre durante los primeros días de vida.

Niños recién nacidos de madres diabéticas han estado pasando hambre y sed durante los dos o tres primeros días de vida, dado que tenían un edema generalizado. Durante este tiempo de completa hambre no hubo tendencia a la hipoglucemia, el nivel de la glucosa en la sangre fué mayor que en los normales recién nacidos. Durante el período de hambre y luego de la administración de agua y alimentos se estudió el balance de electrólitos en algunos casos. Cuando no se daben electrólitos había una continua pérdida de sodio, potasio y cloro, siendo la pérdida del sodio mucho mas grande que la de potasio. En los casos muy edematosos la pérdida de sodio fué muy marcada. No hubo correlación entre la pérdida de potasio y el grado de edema. Immediatamente que se daban electrólitos había una marcada retención de potasio y muy rapidamente los niños habían retenido mas potasio del que existía al nacer. Durante el primer período de retención de potasio había una continua pérdida de sodio. Además la pérdida de sodio era mayor que la de cloro en relación con la composición del líquido extracelular, hecho que indica que en los niños de madres diabéticas existen al nacer grandes cantidades de sodio intracelular. Los valores de suero electrólitos eran normales durante los primeros dos días de vida. Después de la sed y el hambre había siempre una ligera acidosis hiperclorémica. No había signos de hipocalcemia. El agente causante de los des arreglos electrolíticos es discutido. Los resultados son también discutidos con respecto al tratamiento de los niños de madres diabéticas.

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(Head: Professor ARVID WALLGREN)

Studies of the Total Amount of Hemoglobin and the Blood Volume in Children

I. Determination of Total Hemoglobin and Blood Volume in Normal Children

by PETTER KARLBERG and JOHN LIND

The clinical estimation of the total amount of hemoglobin has usually been based on relative hemoglobin values. Hemoglobin concentration measured in fingertip blood is reliable when the blood volume is normal, but contraction or expansion of the blood volume takes place in many disease states. In anemia or polycythemia, for example, the plasma volume will not change sufficiently to compensate for the altered volume of erythrocytes. It is therefore desirable to provide a method for determining accurate total hemoglobin content as a basis for comparison with hemoglobin concentration.

Since 1948 a bloodless method of determining total hemoglobin has been used in the pediatric clinic of Karolinska Institutet. It is a carbon monoxide technique devised by SJÖSTRAND (1948, 1953) for use in adults. For children over three or four years the method can be used as originally described, but it must be modified for use in infants.

The difficulty in obtaining reliable and comparable values of carboxy hemoglobin concentration (COHb) has been the principal objection to the previous methods of blood volume estimation which utilized carbon monoxide. In order to reduce this error, it has been necessary to introduce relatively large quantities of the gas, which immediately creates two serious disadvantages: (1) danger to the patient, and (2) increased absorption by the extravascular tissues, causing a larger margin of error. Sjöstrand's technique obviates this difficulty by using a more sensitive determination of COHb, and by analyzing the respiratory air before and after addition of a known quantity of CO, dispenses with the error caused by the small but variable amount of CO normally present in the blood.

Principle

In Sjöstrand's CO-method of determining total hemoglobin the patient breathes oxygen in a closed system provided with a CO_2 filter until equilibrium is established between the CO-tension of the blood and that of the pulmonary air. As far as the CO in the lungs and the whole system is concerned, is may be regarded as a gas in a tonometer. Therefore the partial pressure of CO in the alveoli can be calculated from the CO concentration in the system. From this figure and the alveolar O_2 pressure, the COHb concentration is calculated. After samples have been taken for these determinations a measured volume of CO is introduced into the system, and after 15 minutes a gas sample is taken for analysis.

From these two CO concentrations in the alveolar air the increase in the concentration of COHb is calculated. Knowing that 1 g hemoglobin requires 1.36 ml CO for 100 per cent saturation, and knowing the amount of CO absorbed by the blood, the total amount of hemoglobin can be calculated. Since the child breathes 90–95 per cent oxygen during the determination and since the CO-meter has a very high sensitivity, a 2–3 % concentration of COHb at the end of the determination is quite accurate and is far below the toxic level.

Methods

In children over 3–4 years

The child breathes through a mouthpiece with valves into a closed system with a CO_2 filter and a communicating rubber bag with a capacity of about 8 litres (Figs. 1 and 2). During the first four or five minutes the system remains open, so the oxygen washes out the nitrogen in the lungs and in the system. Then the system is closed, and the addition of oxygen is stopped. CO from the normally present COHb in the blood passes into the system until equilibrium is established, which occurs in about 10 minutes. After 15 minutes the rubber balloon is detached, by means of a two-way tap, and a new one filled with oxygen is inserted. With the help of a calibrated syringe sealed with oil the system is provided with an accurately determined amount of pure CO, varying from 4 to 14 ml according to the body size and the hemoglobin value expected (approximately the same number of ml as the number of years of age). A higher concentration of CO is obtained in the system, and CO passes from the system to the blood until equilibrium is reached again, which takes another 15 minutes. The two bags are then analyzed for the CO concentration.

In infants.

Through an airtight mask of glass and plastic (Fig. 3) the child breathes into a rubber bag filled with about seven litres of gas. The circulation of gas in the system is maintained by an airtight bellow pump connected to the system in parallel and containing a soda lime filter for the absorption of CO_2 (Figs. 4 and 5). Before the mask is fitted tightly on the child, the system is washed out with pure oxygen. During the

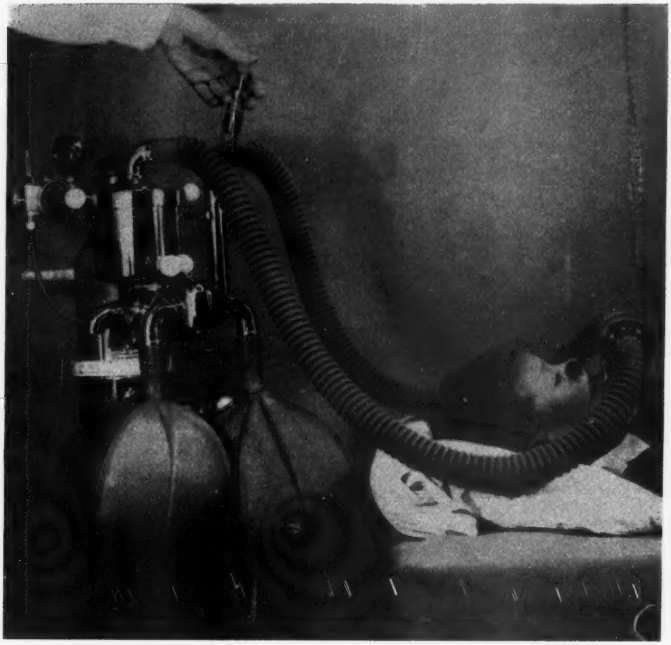

Fig. 1. Determination of total hemoglobin in older children.

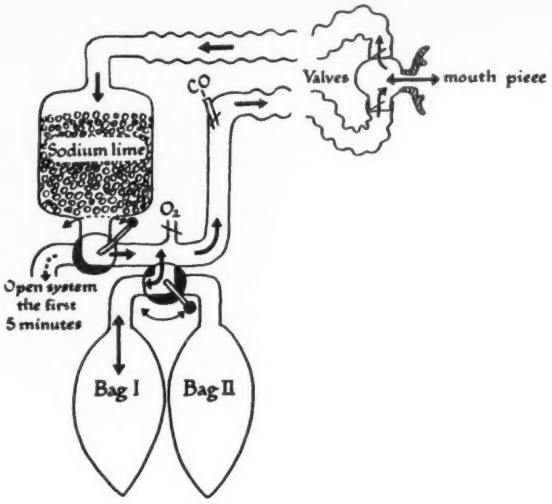

Fig. 2. Schematic diagram of the apparatus.

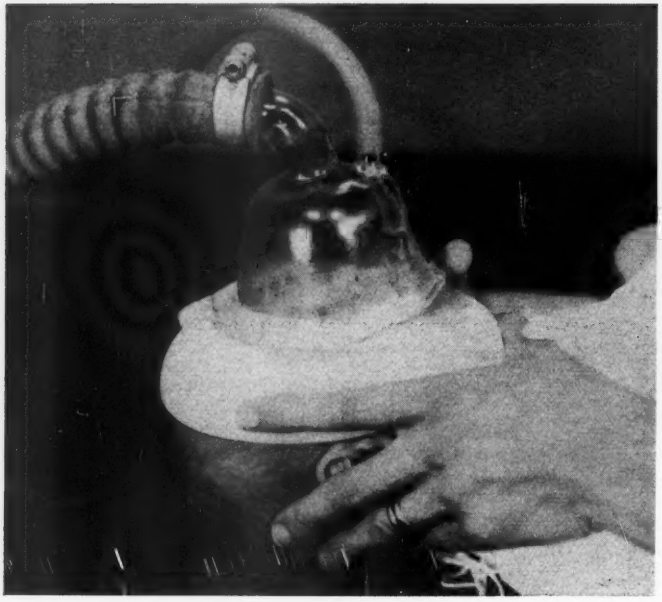

Fig. 3. Plastic-glass mask for infants.

first few minutes the pump forces oxygen through the system, and the air in the respiratory passages of the patient is replaced by oxygen. The system is then closed. In order to determine the amount of CO present in the blood the child first rebreathes only pure oxygen. After 15 minutes the gas equilibrium is reached, and the content of the gas is transferred by the pump to another bag for analysis. The bag is refilled with pure oxygen and the system is again closed. Five to fifteen ml of CO (30 %), depending on the body size and the expected amount of hemoglobin, is introduced into the system with a calibrated syringe. To insure equilibrium of the gases the child now rebreathes for 30 minutes, since the system volume is relatively high compared with the total hemoglobin of the infant. The gas content of the respiratory bag is again transferred for analysis. The volume of the gas left in the bag is measured with a flow-meter.

Analysis of the CO-concentration

The CO content of the two bags is measured by drawing the gas mixture through a CO-meter with a membrane pump at a constant flow of 1 litre/min. The gas mixture passes through a drying agent and a carbon dioxide filter and is then oxidized in a small chamber containing a catalytic agent, Hopacalite. A differential thermometer measures the heat produced, usually recorded over a five-minute period. The apparatus is calibrated before and after, using a gas mixture with a known CO concentration of about 0.01 vol %. From these values the CO concentration in each bag is calculated. The CO-meter permits the analysis of CO concentration with an accuracy of about $\pm$ 0.00015 vol %. (For details see SJÖSTRAND 1948.)

Fig. 4. Determination of total hemoglobin in infants.

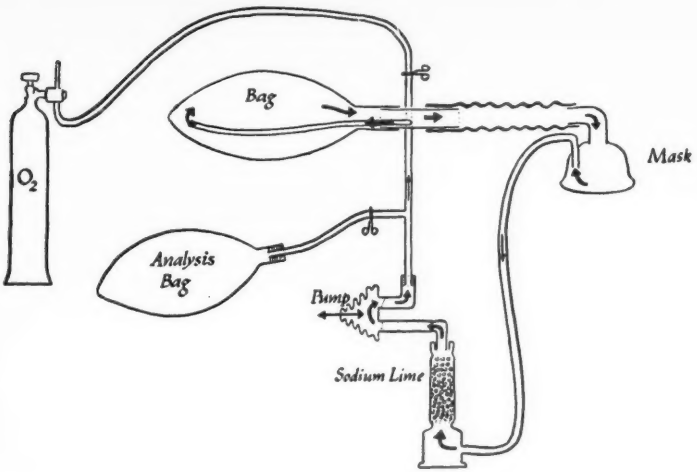

Fig. 5. Schematic diagram of the apparatus.

Calculation of the total hemoglobin

The CO concentration in the system at equilibrium (C_{CO}), before and after the addition of extra CO, is obtained from the gas analysis. From these two values the blood concentration of the COHb at each time is calculated from the formula:

$$\frac{P_{CO}}{P_{O_2}} \cdot K = \frac{COHb}{O_2Hb}$$

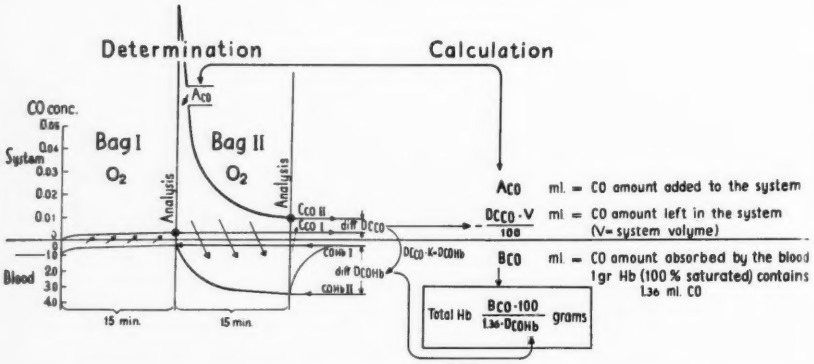

Fig. 6. Schematic diagram of the determination and the calculation of the total amount of hemoglobin (symbols see text).

where P_{CO} and P_{O2} are the partial pressures of CO and O_2 in the respiratory air, and COHb and O_2Hb are the concentrations of carboxy-hemoglobin and oxyhemoglobin in the blood. The constant (K) is calculated from the fact that, with breathing air with a CO concentration of 0.01 vol %, 14 % CO hemoglobin is obtained at equilibrium (SJÖSTEEN and SJÖSTRAND 1951, CARLSTEN, HOLMGREN, LINDROTH, SJÖSTRAND and STRÖM 1954).

As the CO-meter has a high sensitivity (1 part in 1,000,000) and as the patient is breathing a gas mixture with high O_2 tension, it is possible to work with satisfactory accuracy at a concentration of about 0.01 vol % CO. The amount of CO added to the system is thus calculated to give approximately this concentration. In this series it has varied between 0.0080—0.0140 vol %. With these low values of P_{CO} the relationship between COHb and P_{CO} can be approximated in a straight line at constant P_{O_2}. In our calculations we have used for the P_{O_2} a mean value found from direct determinations of the oxygen concentration in the system at several examinations (in older children 92 ± 2 vol %, and 97 ± 1 vol % for infants). As in gas mixtures the ratio between the concentrations of two gases is equal to the ratio between the partial pressures, the formula can be simplified to $COHb = K \cdot C_{CO}$. When C_{CO} is known for the two periods of equilibrations, the increase in concentration of COHb (D_{COHb}) can be calculated (SJÖSTEEN and SJÖSTRAND 1951, CARLSTEN, HOLMGREN, LINDROTH, SJÖSTRAND and STRÖM 1954). Furthermore the results indicate that the proportionality constant (K) is the same in all patients.

The amount of CO absorbed by the blood (B_{CO}) is the difference between the amount of CO added (A_{CO}) and the amount of CO remaining in the system, the latter calculated from the system volume and the CO concentration in the two bags. From the fact that one gram of hemoglobin when 100 % saturated with CO absorbs 1.36 ml of CO, the calculation becomes:

$$\text{Total hemoglobin} = \frac{B_{CO} \cdot 100}{1.36 \cdot D_{COHb}} \text{ g}$$ (for details see SJÖSTRAND 1948). The different procedures of the determination and calculation of the total hemoglobin are presented schematically in Fig. 6.

The error of the method for determination of total hemoglobin in children older than 3 years is calculated from the difference in 49 duplicate determinations[1] and found to be ± 3.5 per cent. In infants it has been found to be ± 7 per cent. (KARLBERG and LIND 1947.)

Discussion of the CO-Method

The method presupposes a normal lung function.

It can be assumed that in 15 minutes the entire amount of blood in the body has time to pass through the lungs and mix well, and that there does not exist any sort of pooling of the blood anywhere in the body (SJÖSTRAND 1948).

That equilibrium between the blood and the system is established after 15 minutes has been determined by continuing the investigation for an additional 15 minutes. For infants the equilibrium is established only after 30 minutes, because the system volume is relatively larger in relation to the blood volume in infants than in older children.

It is assumed that the time required to establish equilibrium is independent of the hemoglobin concentration in the blood. It has been found in adults with polycythemia that the equilibration time is not longer than normal (SJÖSTRAND 1949).

The constant K in the calculation of COHb from P_{CO} in alveolar air (see equation on page 21) is the same for different individuals (CARLSTEN, HOLMGREN, LINDROTH, SJÖSTRAND and STRÖM 1954).

Some CO is absorbed by the myoglobin and the hemoglobin in the blood-producing organs. This absorption is much slower than from the circulating blood. Only after 30 minutes of rebreathing is it necessary to use in adults a 5 per cent correction for the CO absorbed extravascularly (SJÖSTRAND 1953).

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[1] Calculation of the error of the method (δ_x)

$$\delta_x = \pm \frac{\delta_d}{\sqrt{2}}$$

$$\delta_d = \pm \sqrt{\frac{\varepsilon (d^2) - \frac{(\varepsilon d)^2}{n}}{n-1}}$$

d = difference between doubled determinations.

n = number of differences.

δ_d = standard deviation of the differences.

Calculation of Blood Volume

From the total amount of hemoglobin and the hemoglobin concentration in the venous or fingertip blood, the blood volume can be calculated, assuming that the hemoglobin concentration of the blood is the same for the whole body.

$$\text{Blood volume} = \frac{\text{Total hemoglobin} \times 100}{\text{Hb in gram \%}} \text{ ml.}$$

The concentration of the hemoglobin of the fingertip has been determined with a photoelectric colorimeter using 0.015 or 0.025 ml of blood in 5.0 ml of 0.04 % ammonia solution; duplicate determinations were made in each case. The apparatus has been repeatedly standardized with blood of different hemoglobin concentrations by the determination of oxygen capacity by the van Slyke technique. (Professor ENGHOFF in Uppsala performed these analyses.)

When blood volume is calculated from plasma volume or from red cell volume, the hematocrit value and the hemoglobin concentration determined from venous blood or fingertip blood is presupposed to be representative of the blood in the whole body. It is known that the hematocrit value in the venous blood and the fingertip blood is higher than in the capillaries. (Fingertip blood is not capillary blood but comes from the arterioles and

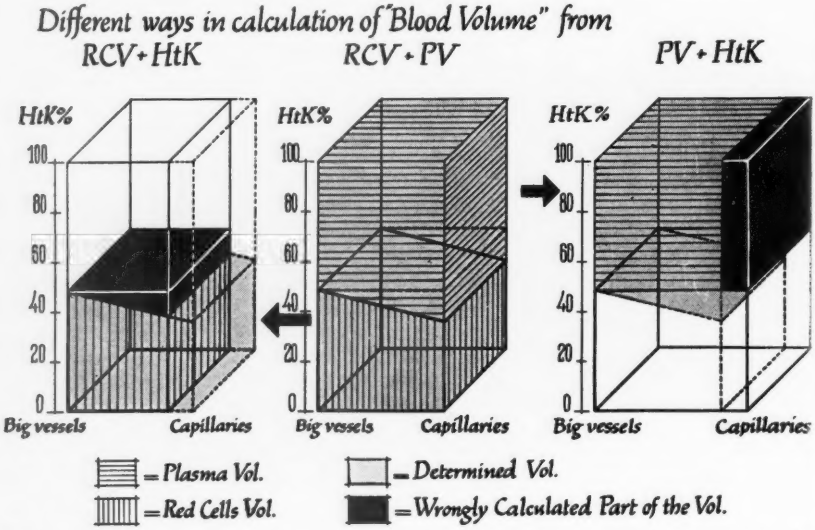

Fig. 7. The influence of the different hematocrit values in vessels of different sizes on the calculations of blood volume.

venules.) This is shown by the calculation of the mean body hematocrit from simultaneously determined plasma volume and red cell volume. (MOLLISON, VEALL and CUTBUSH 1950; KARLBERG and LIND, unpublished).

According to MOLLISON the ratio between the mean body hematocrit and the venous hematocrit is 0.868 in newborns; in adults different authors have found values of 0.70 to 0.95 (MOLLISON-CUTBUSH 1949). Since we have not found any definite figure for this ratio we have not corrected our figures.

If an uncorrected value for the hematocrit is used for the calculation of the blood volume, the plasma volume method will give too high a value and the red cell method too low a value (Fig. 7). Therefore, blood volume calculated from plasma volume cannot be directly compared with that determined from red cell volume. Blood volume calculated from the plasma volume or red cell volume and hematocrit or hemoglobin concentration will give relative values and show the variations in the real blood volume.

Material

A normal material has been examined, consisting of 56 infants and 164 children from the age of 3 years to puberty, 87 boys and 77 girls. The determinations were carried out on healthy school and day nursery children and on children admitted to the hospital for disturbances which could not influence the mass or composition of the blood.

These patients had a body constitution which can be considered normal for Swedish children according to a Swedish growth chart (KARLBERG and IGGBOM 1951), Fig. 8.

Results

The data obtained were charted against age, body weight, body length, and body surface area.

Age.—The values obtained for the total amount of hemoglobin and calculated blood volume obviously vary with age because of marked progressive increase in body size associated with growth.

Body weight.—The data plotted against the body weight, the most commonly used measurement of the body size, are shown in Figs. 9 and 10. Since there is no tendency to a difference between the sexes in the first year of life, males and females were not charted separately. Beginning at a body weight of about 20 kg there is a tendency toward a difference in the values obtained for the two sexes, a difference which increases with age and becomes marked at puberty. This corresponds to SJÖSTRAND's data (1953). Fig. 10 also shows an almost rectilinear relationship between blood volume and weight up to about 20 kg; thereafter the blood volume increases more rapidly than the weight but retains a rectilinear relationship.

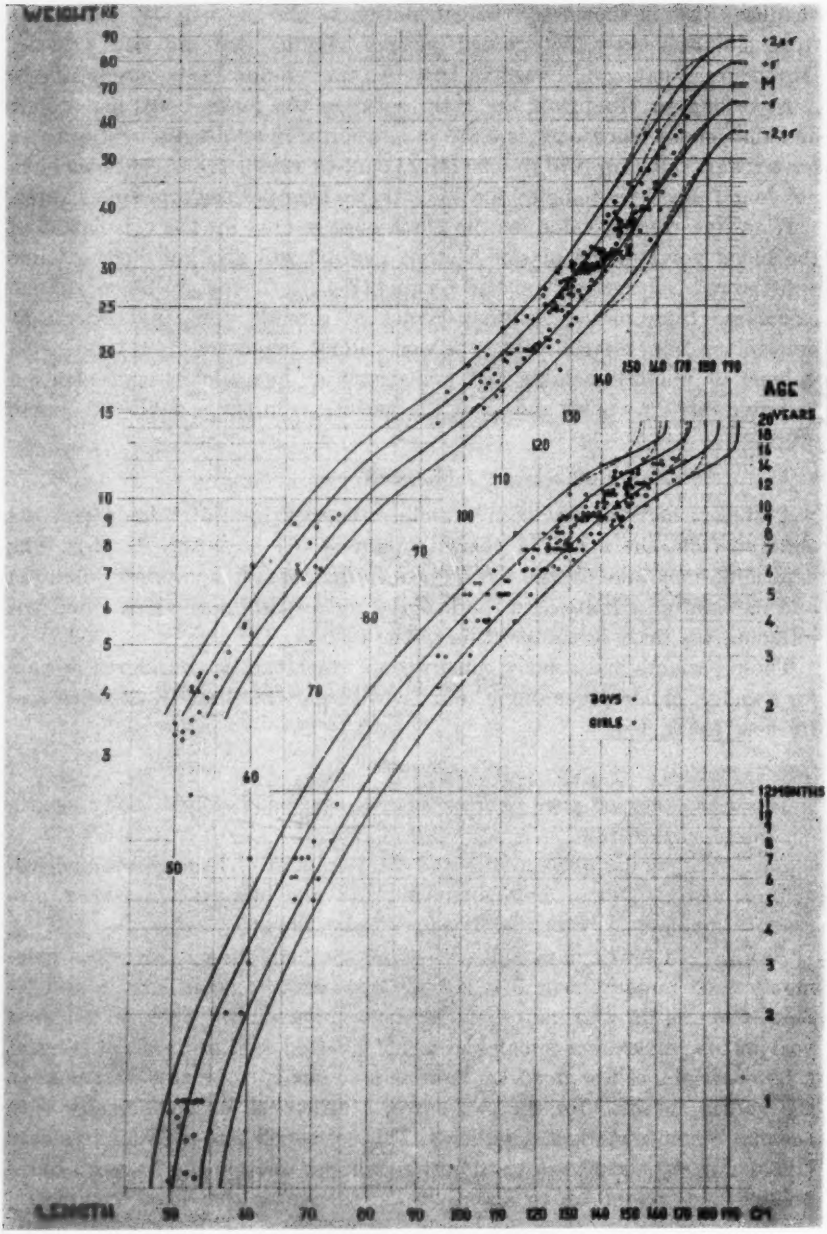

Fig. 8. The material plotted in a Swedish growth chart showing the relationship between age and height and the relationship between height and weight in comparison to the normal variations.

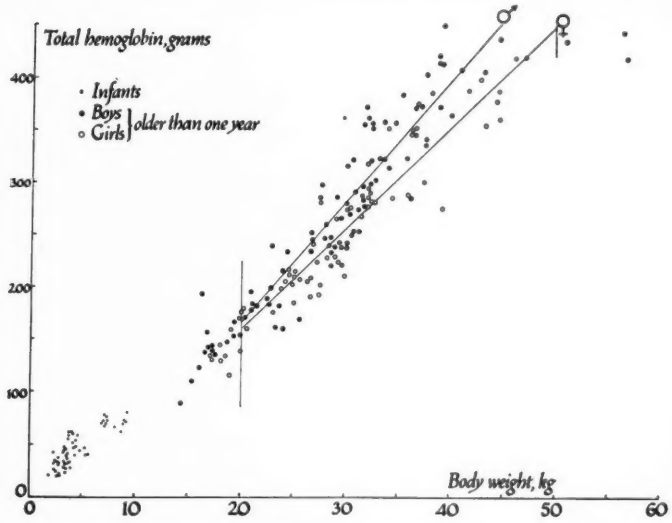

Fig. 9. The relationship between total hemoglobin and body weight with calculated regression lines according to Table 1.

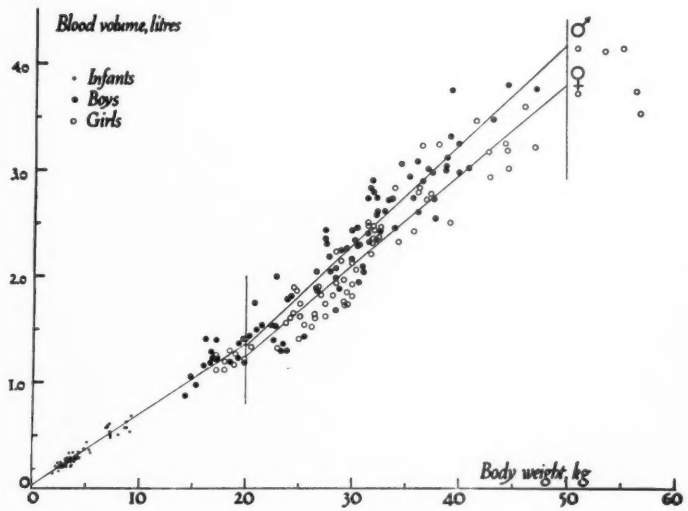

Fig. 10. The relationship between blood volume and body weight with calculated regression lines according to Table 1.

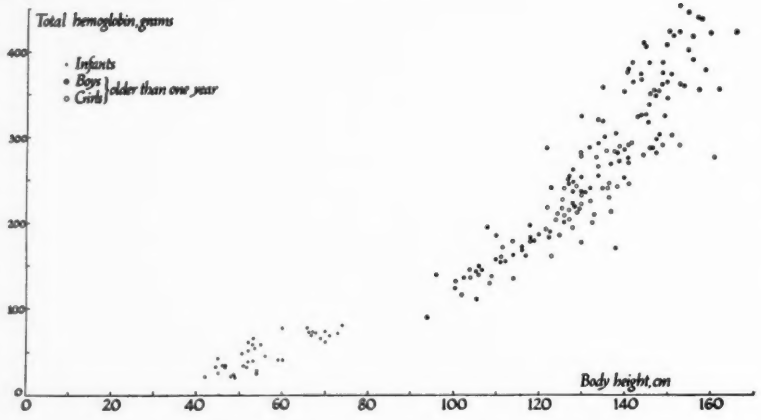

Fig. 11. The relationship between total hemoglobin and body height.

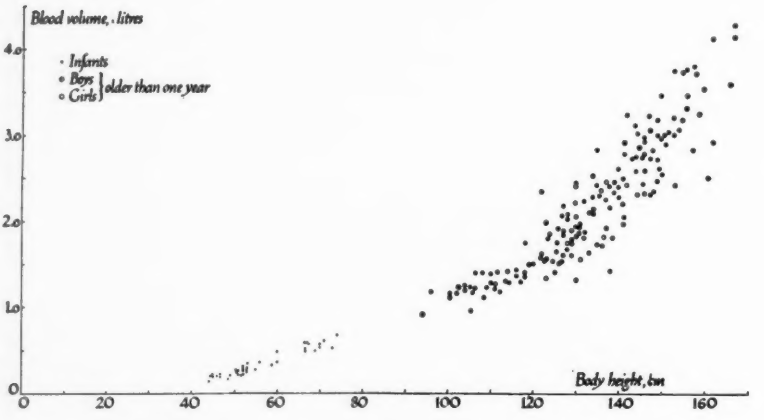

Fig. 12. The relationship between blood volume and body height.

The correlation between total hemoglobin and weight is not so obvious (Fig. 9).

Body length (length for the infants and height for the older children).—A curvilinear relationship is obtained, when body length is used as the correlating factor (Figs. 11 and 12), since increase in length does not keep pace with increase in weight during growth. This is unsatisfactory as a practical correlation factor.

Body surface area.—Body surface area, calculated according to the Du Bois height-weight formula, is often used as a measure of the body size.

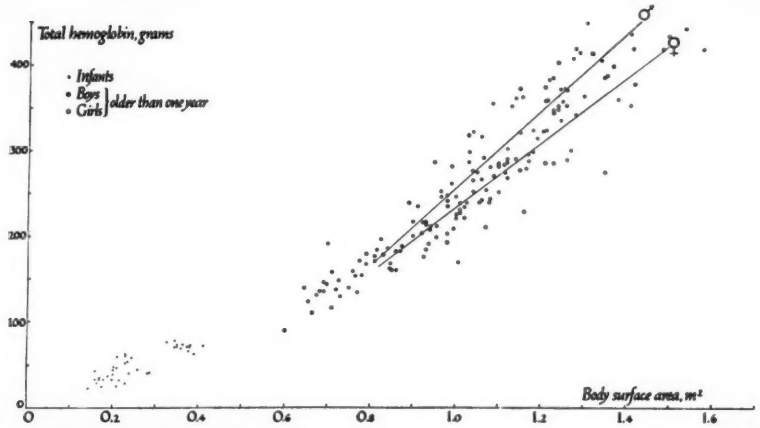

Fig. 13. The relationship between total hemoglobin and body surface area (Du Bois' height-weight formula) with regression lines according to Table 1.

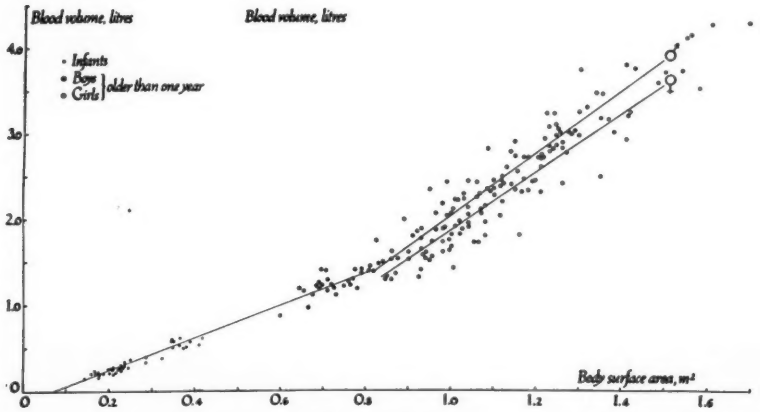

Fig. 14. The relationship between blood volume and body surface area (Du Bois' height-weight formula) with regression lines according to Table 1.

When total hemoglobin and blood volume are plotted against surface area, the results are similar to those obtained with body weight, a steady increase during the entire period of growth (Figs. 13 and 14).

Statistical treatment.—According to the trends of the above-mentioned relationships the material has been divided into three groups: (1) infants and children under 20 kg body weight, and (2) boys and (3) girls over 20 kg. In each group regression calculations according to SNEDECOR (1950) were done on the relationships between the total hemoglobin and blood volume

TABLE 1

The regression calculations (according to SNEDECOR 1950).

	Number	Equations	δ_{y-Y}	ε_b	ε_{x_0}	r	ε_r
Children with body weight 20.0–50.0 kg							
Boys Total Hb/weight	72	$Y = 11.71\ x - 69$	30.3	0.584	18.7	0.922	0.0177
Total Hb/surface area . . .	72	$Y = 453.6\ x - 199$	30.7	23.1	25.6	0.922	0.0177
Blood volume/weight	72	$Y = 0.094\ x - 0.55$	0.225	0.00436	0.138	0.932	0.0154
Blood volume/surface area .	72	$Y = 3.662\ x - 1.62$	0.223	0.168	0.186	0.934	0.0151
Girls Total Hb/weight	60	$Y = 9.72\ x - 35$	22.9	0.452	14.6	0.931	0.0173
Total Hb/surface area . . .	60	$Y = 377.4\ x - 144$	29.8	23.6	26.3	0.903	0.0239
Blood volume/weight	60	$Y = 0.085\ x - 0.46$	0.378	0.00746	0.240	0.831	0.0399
Blood volume/surface area .	60	$Y = 3.335\ x - 1.45$	0.394	0.311	0.347	0.815	0.0433
Children with body weight under 20 kg							
Boys + girls							
Blood volume/weight	80	$Y = 0.066\ x + 0.037$	0.0637	0.00120	0.0128	0.987	0.00281
Blood volume/surface area . . .	64	$Y = 1.890\ x - 0.141$	0.0656	0.0354	0.0174	0.989	0.00265

and the body weight and body surface area, except for the total hemoglobin in the first group. During this part of life the hemoglobin concentration varies so much that a rectilinear relationship cannot be expected. The results are given in Table 1.

Discussion

For comparison of normal individuals of different ages, body weight seems to be the most applicable correlating factor, even though it will be influenced by the fact that constitution may vary during development. For studies covering a period of growth extending over several years, the Du Bois height-weight formula is not suitable as a correlating factor. This formula is based on direct determinations of the surface area of not more than ten cases, including a malformed child, an adult dwarf, an athletic youth and an obese old woman, the remaining cases all being 18–32 years of age (Du Bois and Du Bois 1915, 1916). This formula has, however, been found applicable in the study of individuals all belonging to the same age group but having different body constitutions.

Relationship of total Hb and blood volume to body size

The figures and the regression calculations have shown a good correlation between total hemoglobin and blood volume and the body size as represented by the body weight during childhood. This correlation, however, changes during growth.

Relationship of total Hb and blood volume to age

In order to study the influence of age on total hemoglobin and blood volume the material has been divided into different age-groups and the mean value of total hemoglobin and blood volume per kg body weight has been calculated for each group (Table 2). The total hemoglobin per kg diminishes during the first years of life, reaches a minimum at 3 to 6 years, and then increases again. This general tendency is demonstrated in spite of the fact that some of the children exhibited different degrees of body development. This could be explained by the fact that hemoglobin concentration decreases during the first months of life and increases slowly thereafter (significant rise occurs at 6–7 years of age; finally there is a sharp increase in boys at puberty). This explanation is not sufficient because the relationship between blood volume per kg and age is similar but less striking. The total hemoglobin and blood volume per kg reaches a minimum at 3 to 6 years of age in spite of the fact that children at this age have less subcutaneous tissues (Stuart and Sobel 1946).

TABLE 2

The relationship of total Hb/kg and blood volume/kg to age.

Age group years	Number		Total Hb/kg		Blood volume/kg	
	Boys	Girls	Boys	Girls	Boys	Girls
$^{1}/_{12}\rightarrow$	11		10.0		.072	
$^{2}/_{12}-{}^{5}/_{12}$	5		9.2		.073	
$^{6}/_{12}-{}^{11}/_{12}$	10		9.0		.070	
3	3	—	7.6	—	.068	—
4	6	2	7.7	7.6	.067	.064
5	6	7	8.2	7.7	.064	.066
6	5	6	9.0	7.6	.065	.064
7	15	12	8.7	8.4	.069	.068
8	8	7	9.0	8.4	.076	.069
9	11	16	9.2	8.5	.076	.068
10	9	8	10.5	8.6	.080	.073
11	9	6	10.1	9.1	.079	.074
12	9	3	9.4	8.8	.078	.073
13	3	5	10.5	9.1	.085	.077

Relationship of total Hb and blood volume to rate of growth

The increases in the total hemoglobin and blood volume seems to be inversely proportional to the rate of growth (increasing body weight per kg per year, according to WETZEL 1951). After the age of 3 years, the lowest total hemoglobin/kg and blood volume/kg occur during the period of greatest increase in growth during childhood. The blood values remain low during the second acceleration of growth, at 6–7 years. At the end of this period, when the rate of growth slows down, the blood values increase again. Children with orthostatism, in whom the rate of growth has been high for a prolonged period, have been found to have lower than normal values for total hemoglobin/kg and blood volume/kg (KARLBERG and LIND 1950).

Summary

A bloodless method of CO determination of the total amount of Hb which was described by SJÖSTRAND has been used in older children and modified for use in infants. The error of the method has been found to be ± 3.5 per cent for children aged 3–14 years, and ± 7 per cent for infants. The blood volume has been calculated from the total Hb and the Hb concentration in the fingertip blood.

A normal material has been examined, consisting of 56 infants, and 87 boys and 77 girls aged 3–14 years. The values found have been correlated with kilograms o

body weight. In order to be able to compare these values with those from children with a body constitution differing from normal, the material has also been correlated with the body surface area calculated according to the Du Bois height-weight formula. For comparison of different ages the body surface area seems to be an unsatisfactory criterion of body size. The investigations have shown that the difference between the sexes becomes more marked with age. Total Hb and blood volume per kg of body weight show changes during growth, and their connection with variations in the rate of growth are discussed.

Etude de la quantité totale d'hémoglobine et du volume du sang chez l'enfant.

Une méthode pour la détermination de l'oxyde de carbone de la quantité totale d'hémoglobine, n'employant qu'une petite quantité de sang et décrite par SJÖSTRAND, a été utilisée chez des enfants plus grands et modifiée pour son application aux nourrissons. On a trouvé que l'erreur de la méthode était de ± 3,5 % pour des enfants âgés de 3 à 14 ans, et ± 7 % pour des nourrissons. Le volume du sang a été calculé à partir de l'hémoglobine totale et de la concentration de l'hémoglobine du sang pris au bout du doigt. L'auteur a examiné des sujets normaux, comprenant 56 nourrissons et 87 garçons et 77 filles âgés de 3 à 14 ans. Il a établi une relation entre les valeurs trouvées et le poids du corps exprimé en kilogrammes. Afin de pouvoir comparer ces résultats avec ceux provenant d'enfants ayant une constitution corporelle différente de la normale, il a établi également une relation avec la surface corporelle calculée d'après la formule taille-poids de Du Bois. Pour comparer différents âges, la surface corporelle donne une évaluation incomplète de la grandeur du corps. Cette étude a montré que la différence entre les sexes s'accentuait au fur et à mesure que l'âge avançait. La quantité totale d'hémoglobine et le volume du sang par kilogramme de poids corporel changent pendant la croissance. L'auteur discute le rapport entre ceux-ci et les variations dans le taux de croissance.

Untersuchungen über die totale Hämoglobinmenge und das Blutvolumen bei Kindern.

Eine unblutige Methode der CO-Bestimmung der totalen Hämoglobinmenge, die von SJÖSTRAND beschrieben worden ist, wurde bei älteren Kindern angewandt und für Kleinkinder modifiziert. Die Fehlerquelle der Methode betrug ± 3,5 % bei Kindern im Alter von 3–14 Jahren, und ± 7 % bei Kleinkindern. Das Blutvolumen wurde aus dem Totalhämoglobin und der Hämoglobinkonzentration bestimmt. Die Blutprobe wurde aus der Fingerblume entnommen. Ein Normalmaterial von 56 Kleinkindern, und 87 Knaben und 77 Mädchen im Alter von 3–14 Jahren wurde untersucht. Die gefundenen Werte wurden in Beziehung zum Körpergewicht in kg gesetzt. Um diese Werte mit denen solcher Kinder mit einer vom Normalen abweichenden Körperkonstitution vergleichen zu können, wurde das Material auch zur Körperoberfläche, nach der Länge–Gewicht Formel von Du Bois berechnet, in Beziehung gesetzt. Zum Vergleich verschiedener Altersgruppen scheint die Körperorberfläche ein unzureichendes Kriterium der Körpergrösse zu sein. Die Untersuchungen haben gezeigt, dass der Geschlechtsunterschied mit zunehmendem Alter mehr ausgeprägt ist. Die totale Hämoglobinmenge und das Blutvolumen per kg Körpergewicht zeigen Schwankungen während des Wachstums, und ihre Beziehung zu Variationen in der Wachstumsgeschwindigkeit werden diskutiert.

Estudio de la determinación de la cantidad total de hemoglobina y del volumen sanguíneo en niños.

El método, sin obtención de muestras de sangre, para determinaciones de la cantidad total de Hb por el CO, descrito por SJÖSTRAND, se usó en niños mayores y se modificó para usarlo en lactantes. El error encontrado para el método fué de ± 3,5 % para niños de 3 a 14 años de edad y de ± 7 % para lactantes. Se calculó el volumen de sangre por el total de Hb y la concentración de Hb en la sangre de la punta de un dedo. Se examinó un material normal que consistía en 56 lactantes y 87 niños y 77 niñas de 3 a 14 años de edad. Los valores hallados se correlacionaron con el peso en kilogramos. Con el fin de poder comparar estos valores con aquellos de niños con una constitución corpórea distinta de la normal, se correlacionaron los hallazgos con la superficie corporal, calculada en relación con el peso y la altura de acuerdo con la fórmula de Du Bois. Para comparar las diversas edades, parece que la superficie corporal constituye un criterio no satisfactorio de las proporciones corporales. Las investigaciones han mostrado que las diferencias entre los sexos vuélvensen màs acentuadas con los años. La Hb total y el volumen sanguíneo por kilogramos de peso, presenta modificaciones durante el crecimiento y se discute sus variaciones con la rapidez del crecimiento.

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(Head: Prof. Dr S. VAN CREVELD)

Genital Intersexuality in Three Brothers, Connected with Consanguineous Marriages in the Three Previous Generations

by O. M. DE VAAL

The problem of the sexual determination in cases of clinical intersexuality cannot be solved directly by estimation of the chromosomal constellation of the cells of the individual. A few months ago a method was described which was based on differences in the nuclear mass of male and female cells (epithelium of skin); experiences with this method, however, are very scanty (6).

Clinically, a diagnosis must be made by indirect means, based on a conception that seems to fit best to the special problems. My own conception (1949) was developed to be used for clinical cases of intersexuality (9).

Several facts of fundamental importance are considered in this hypothesis, e.g. the possibility that an ovary can appear in a testicular form, whereas the reverse is not known in animals with a comparable relation of the sex-chromosomes as is encountered in man (amphibia, mammals).

The knowledge derived from experimental intersexuality in numerous species of mammals indicates that only the female genital tract, and not the gonads, responds to androgens. Reactions of the male ducts to oestrogenic substances are of minor importance only.

The disturbances of the development of the gonads and genital ducts, including the external genital organs, are preferably called gonadal and genital intersexuality, respectively. Both forms may occur simultaneously or separately.

Clinically the following differentiation may be made:

A. *In females.*

1. *Hormonal (humoral) intersexuality, based on congenital adrenocortical hyperplasia.* — A recessive genetic factor is generally held responsible for the syndrome. This form of intersexuality is merely genital in character. An androgenic tumour (arrhenoblastoma) of the mother has been reported as a very rare cause (2).

New interest in this form of intersexuality is aroused by the modern treatment of congenital adrenocortical hyperplasia with cortisone (8, 12).

2. *Genetic, gonadal or gonadogenital intersexuality.*—In this category cases such as the so-called "adenoma tubulare" are included.

When the gonadal intersexuality is only partial, ovo-"testes" or unilateral ovary and "testis" are seen; such cases are accompanied by more or less severe intersexual disturbances of the genital tract and external organs.

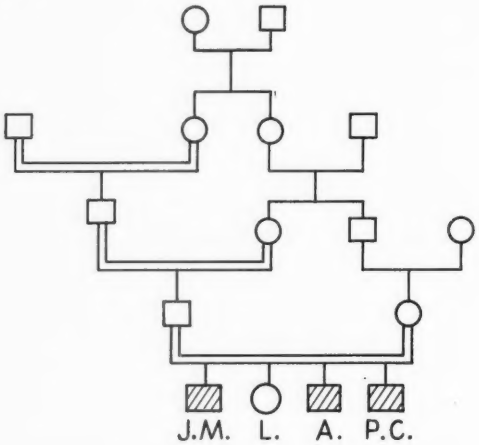
3. *Genetic, genital intersexuality.*—In this group, a type with the urethra ending in the vagina is sometimes described. Ordinarily, the upper part of the vagina ends in the urethra, as in all cases of hormonal intersexuality. The first form, however, gives rise to severe urological complications (5). It is theoretically possible that in this group of intersexual disturbances cases of congenital adrenocortical hyperplasia occur, which were "cured" before parturition (WILKINS (11)).

B. Genetic, genital intersexuality in males.

The slightest forms are known as hypospadia. In more severe cases the scrotum is fissured, giving the impression of two "labiae". The urethra ends under the hypoplastic penis, which has a clitoris-like appearance in most cases. Under the urethral orifice a short, proximal blindly ending canal, the rest of the urogenital sinus, may be seen. It is the equivalent of the distal part of the vagina in the female. The external organs are so much female-like that most of the children are considered to be females and grow up as such. Internally more or less well-developed parts of the Müllerian duct (upper part of vagina, uterus, tubae) may be found.

For the familiar relationship of cases of intersexuality the work of GATES (4) gives ample information. Valuable details are dealt with also by RHODES (7), COLLIER (3), BIGGS c. s. (1). Sometimes, however, it is difficult to judge from the paper concerned the exact form of intersexuality which is considered.

This report concerns three brothers, 6, 3 and $\frac{1}{2}$ year old, when seen for the first time; there were consanguineous marriages in three previous generations (see pedigree).



The parents, one pair of grandparents and one pair of great grandparents are cousins.

The child J.M. was raised as a girl, although the parents were aware of some abnormality. The child L. was a normally developed girl. The child A. was considered to be a female on the first day of life, because the penis was only the size of a clitoris, but the absence of a vaginal canal and the nearly normal scrotum with both testicles descended, changed the parents' mind, and he was raised as a boy. The child P.C. was just like the oldest child J.M. and considered to be a girl, but the finding of both testicles in the "labiae" at the age of 6 months was the cause of an investigation of all the children of the family.

The child J. M. was 6 years old on admission and had been raised as a girl. The behaviour was always quite normal for a girl, except for a tendency to pass water in a standing position when with "her" male playmates. There were no abnormal findings on physical examination, except for the genital organs. The mons veneris was somewhat prominent, the formation of the external organs was completely female, except for the skin of the "labiae" which had a scrotal character. In the left "labium" a distinct testicle could be felt, of normal shape and consistency. A cremaster reflex could be elicited. On the right side, no gland could be palpated, but after treatment with chorionic gonadotropic hormone, 6×100 and 6×500 I.U., in six weeks, the right testicle descended. Further treatment consisted in transformation into a boy. The child accepted the metamorphosis without serious disturbances, and up to this time (he is now 11 years old) no difficulties have been encountered.

The boy A. had a less serious abnormality; the penis was severely hypoplastic, and the urethral orifice was at the basis of this organ; the scrotum had developed practically normally.

The child P.C., 6 months old when seen first, resembled the oldest child J.M. in every respect, only the testes were already completely descended.

Diagnostically, hormonal intersexuality could be excluded for several reasons: testicles in the "labiae", no signs of virilisation or metabolic disturbances. There were no elevated levels of 17-ketosteroids in the urine. Furthermore, there was one unaffected female child.

Gonadogenital forms, very rare in comparison with other forms, seemed unlikely because of the unaffected female and in view of the whole clinical picture.

The slight affection of boy A. was an indication for the true nature of the abnormality; his brothers showed only a more severe form of developmental disturbance. No further exploration of the intra-abdominal sex organs has been carried out. It is possible that a recessive hereditary factor

is responsible, just as in cases of hormonal intersexuality. The three consanguineous marriages might be responsible for the fact that the factor is brought to the surface.

Surgical correction, so far as possible in so severe cases of hypoplasia of the external organs, will be carried out at a time when the pragmatic sex, i.e. the experienced and wanted sex of the patient, agrees with the real (or presumed) sex. One must always keep in mind that "despite careful plannings in childhood, embarrassing developments may occur during adolescence. For this reason it is probably better to postpone some of the more radical operations or plastic conditions until puberty" (WILKINS).

Summary

On the basis of experimental and spontaneously occurring disturbances in the development of the gonado-genital tract the clinical forms of intersexuality are classified. Data on the genetic background of all forms of intersexuality in man are few.

An unusual case of genital intersexuality in three brothers who had a normally developed sister, is described. In three preceding generations, consanguineous marriages had occurred.

The various therapeutic measures are mentioned; care must be taken with operative support before puberty.

Intersexualité chez trois frères en rapport avec des mariages consanguins dans les trois générations antérieures.

Les différentes formes d'intersexualité sont classées par rapport à des faits expérimentaux et des cas cliniques spontanés se rapportant aux erreurs de développement du tractus génital. Les fondements génétiques de toutes les formes cliniques d'intersexualité sont peu nombreux. L'auteur décrit un cas exceptionnel d'intersexualité chez trois frères qui ont d'ailleurs une sœur normale. Dans les trois générations antérieures il y avait des mariages consanguins. Les différentes thérapeutiques sont signalées. Il faut être très circonspect lorsque l'on envisage une opération avant la puberté.

Genitale Intersexualität bei drei Brüdern, verbunden mit Blutsverwandtenehen in drei vorhergehenden Generationen.

Auf der Basis von experimentellen und spontan auftretenden Entwicklungsstörungen des Gonado-genitaltraktes werden die klinischen Formen der Intersexualität klassifiziert. Es gibt nur wenige Angaben über die Genese aller Formen von Intersexualität beim Menschen. Ein ungewöhnlicher Fall von Intersexualität bei drei Brüdern, die eine normal entwickelte Schwester hatten, wird beschrieben. In den drei vorhergehenden Generationen waren Blutsverwandtenehen aufgetreten. Die verschiedenen therapeutischen Massnahmen werden angegeben; vor der Pubertät ist Vorsicht mit operativen Eingriffen angezeigt.

Intersexualidad genital en tres hermanos relacionada con matrimonios consanguíneos en las tres generaciones anteriores.

Las formas clínicas de intersexualidad están clasificadas sobre la base de los cambios experimentales o clínicos durante el desarrollo del tracto gonadogenital. En el hombre

existen pocos datos acerca del fondo genético de todas las formas de intersexualidad. Se describe el caso poco común de intersexualidad genital en 3 hermanos que tuvieron una hermana normalmente desarrollada. En las tres generaciones anteriores existieron matrimonios consanguíneos. Se mencionan medidas terapéuticas. Debe tenerse cuidado con las soluciones quirúrgicas anteriores a la pubertad.

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Incidence of Hypertrophic Pyloric Stenosis in the Various Jewish Communities in Israel

by ZWI LARON

Many authors who deal with hypertrophic pyloric stenosis are of the opinion that there is a difference in the distribution of this disease among different races and even in different countries. As WALLGREN writes, it seems that hypertrophic pyloric stenosis is common among Anglo-Saxons, but relatively rare in Latin races. The same author cites the report of ECKSTEIN who found only two cases among 50,000 children examined in Turkey, the parents of these two being foreign-born. A medically trained monk found only one case in the Belgian Congo during many years, this patient being of French parentage. FIELD reported that the disease is exceedingly rare in Malaya where only two cases were recorded among 222,782 live births in the year 1949. Many authors from the U.S.A. (4, 6, 7) writing about hypertrophic pyloric stenosis report contradictory data on the incidence of this disease among Negroes. No paper gives the correlation between the incidence and the Negro population of the district concerned. In many textbooks we can still read about the rarity of this condition among them.

We thought it would be interesting to study the distribution of hypertrophic pyloric stenosis in our country, where the different communities coming from three and more continents represent good material for comparison.

It is relevant to note that the population originating around the Mediterranean Sea exhibits some common hematologic disorders, e.g. Cooleys anemia, favism, hemolysis due to sulfa drugs or typhoid. It is possible that this population also has other common characteristics.

Material

We gathered all the cases of hypertrophic pyloric stenosis from all the pediatric departments in Jewish hospitals in Israel,[1] for the period of 1930–1953. Not included are 36 cases where charts were not found, details not complete or diagnosis uncertain,

[1] Even before the establishment of the State of Israel in 1948, the Jewish population was concentrated in the present areas of the State; therefore this would not make any difference to the data presented.

and 2 cases admitted to the hospitals of Tiberias and Ber-Sheba. Altogether there were 271 cases, 7 of them being non-Jews.

The Jewish population of Israel was 700,000 in 1948, and doubled after the State's independence as a result of the large immigration of Jews from Europe, Asia and North Africa. All the Jews originated in these continents; those living in America, Australia etc. are emigrants from the above-mentioned parts of the world or their descendants.

We divided the Jewish population into four communities: *Ashkenazi*—Jews originating from Europe except for Spain, Holland, Bulgaria, Jugoslavia and Greece. *Sephardi*[1]—originating from Spain, Holland, Bulgaria, Jugoslavia, Greece, Turkey, Syria and part of Lebanon. *Oriental*—coming from the other Arab countries, Persia, Kurdistan, India and North Africa. *Yemenite*—a closely knit Jewish community from Yemen, whose origin is still not quite established. We therefore separated this group from the oriental Jews.

Method

We divided the cases into two groups consisting of (1) 200 cases on whom operation was performed and hypertrophy of the pylorus found; to this group belong also four cases in whom hypertrophic pyloric stenosis was found at autopsy; and (2) sixty-four cases clinically diagnosed and not operated.

The distribution of the communities within the population was taken from the booklet "Immigration in Israel" 1953, by Dr. B. GIL. Because of the difference in composition of the Jewish population before and after the big immigration, we divided the cases into two periods: before and after this event. We took the distribution in the year 1943 as a sample of the first period, and the year 1952 to reflect the present distribution of the Jewish communities in Israel.

Results

1. *Distribution*

In comparing the distribution of hypertrophic pyloric stenosis in the different communities according to the two periods, we came to the conclusion that the disease was almost equally frequent in each group of Jews, as may be seen from the following table.

	Ashkenazi			*Sephardi*			*Oriental*			*Yemenite*		
	% of tot. J. popul.	% of operated cases	% of non-oper. cases	% of tot. J. popul.	% of operated cases	% of non-oper. cases	% of tot. J. popul.	% of operated cases	% of non-oper. cases	% of tot. J. popul.	% of operated cases	% of non-oper. cases
1930–1948	79.4	82.5	72.2	8.8	5.5	8.3	7.1	4.6	11.1	4.7	2.7	2.7
1949–1953	58	81.2	63.3	12	5.2	6.6	23	10.4	23.3	7	3.1	6.6

[1] Jews whose forefathers had been resident in Spain, and even to-day may speak Spanish.

2. *General incidence*

During the period of 1948–1953 there were 196,587 Jewish births in Israel. In the same period there were 108 operated cases of hypertrophic pyloric stenosis including the cases operated without detailed case histories. This would give an incidence of 0.05 %. Adding the non-operated cases the incidence rises to 0.06 %. WALLGREN, among 25,642 births during 6 years in Gothenburg found an incidence of 0.4 %. DAVISON estimated that the incidence of hypertrophic pyloric stenosis in Newcastle was about 0.3 %.

3. *Sex*

The sex distribution among the different communities was quite constant, the males constituting 76–82 % of the total number of cases. Because of the small number of cases, it is difficult to assess whether the higher percentage of males among the Yemenite Jews is of any statistical importance.

Hypertroph. pyl. sten.	Number of cases	% males
Operated, total	200	78
Non-operated, total	64	78.7
Ashkenazi		
operated	168	76
non-operated	45	82
Sephardi		
operated	11	81
non-operated	7	80
Oriental		
operated	15	80
non-operated	11	63
Yemenite		
operated	6	100
non-operated	3	88

The figures are in accordance with the reports in the literature: FREDEEN, 78 %; HOLT, 80 %; LADD, 85 %; SCHAEFER, 86 %; WALLGREN, 80 %.

The diagnostic problems of this disease as brought out by this study will be published separately.

Summary and Conclusions

An attempt is made to see whether there are any differences in the distribution of hypertrophic pyloric stenosis in the various communities of the Jewish population in Israel, 264 cases being studied. It was found that the general incidence of this disease is very low, being 0.05 % of cases proved by operation or autopsy, and 0.06 % when including the clinically diagnosed ones.

The distribution of hypertrophic pyloric stenosis is similar in the different communities. Since they come from three different continents, it would seem that there is no climatic influence on the etiology of this disease. It would be interesting to do a study in another country with a Jewish population in order to compare the incidence of this disease among these Jews and the general population, and thereby determine whether the low incidence found by us is due to ethnographic reasons.

Fréquence de la sténose hypertrophique du pylore chez les différentes communautés juives d'Israël.

L'auteur a tenté de voir, par l'étude de 264 cas, s'il y avait quelques différences dans la distribution de la sténose hypertrophique du pylore dans les différentes communautés de la population juive en Israël. Il a trouvé que la fréquence générale de la maladie était très basse: 0,055 % des cas vérifiés à l'opération ou à l'autopsie, et 0,06 % en y incluant les cas dont on a fait le diagnostic par la clinique. La répartition des cas de sténose hypertrophique du pylore est la même dans les différentes communautés. Puisqu'ils sont venus de trois continents différents, il semblerait que le climat n'a pas d'influence sur l'étiologie de la maladie.

Die Häufigkeit der hypertrophischen Pylorusstenose in den verschiedenen jüdischen Gemeinschaften in Israel.

Es wird der Versuch gemacht, festzustellen, ob irgendein Unterschied in der Verteilung der hypertrophischen Pylorusstenose in den verschiedenen Gemeinschaften der jüdischen Bevölkerung in Israel besteht. 264 Fälle wurden untersucht. Man fand, dass die Anzahl der Fälle sehr gering ist und nur 0,055 % bei den durch Operation oder Obduktion bestätigten Fällen beträgt, und 0,06 % wenn man die klinisch diagnostizierten mitrechnet. Die Verteilung der Pylorusstenose ist gleich in den verschiedenen Gemeinschaften. Da sie aus verschiedenen Kontinenten kommen, scheint es, dass klimatische Einflüsse für die Ätiologie keine Rolle spielen.

La distribución de estenosis pilórica hypertrófica en diversas comunidades judías en Israel.

Se hizo una tentativa para ver si hay alguna diferencia en la distribución de estenosis pilórica hipertrófica en diversas comunidades de población judía en Israel. Se estudiaron 264 casos. Se encontró que la incidencia general de esta enfermedad es muy baja, siendo de 0,055 % de casos comprobados en la operación o en la autopsia y de 0,06 % cuando se incluyen los casos diagnosticados clinicamente. La distribución de la estenosis pilórica es semejante en las diferentes comunidades. Dado que ellas provienen de tres continentes diferentes parecería que no hay influencia climática en la etiología de la enfermedad.

Acknowledgement

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Primary Vitamin D Refractory Rickets

II. Metabolic Studies during Treatment with Massive Doses of Vitamin D

by R. ZETTERSTRÖM and J. WINBERG

In primary vitamin D refractory rickets the changes in calcium and phosphate metabolism are roughly the same as those found in vitamin-deficiency rickets. The absorption of calcium from the gut is extremely low as is the urinary excretion. The concentration of calcium in the serum is, however, normal or only slightly reduced. There is a marked hypophosphatemia but the absorption of phosphate from the gut is unimpaired when there is a suitable Ca:P ratio in the diet. The urinary excretion of phosphate varies directly with phosphate absorption (GUNTHER, COHN, COHN & GREENBERG). Thus, the calcium clearance is extremely low at the same time as the phosphate clearance in some cases is elevated.

The etiology of primary vitamin D refractory rickets is still obscure. As far as is known, the disease is not secondary to nutritional deficiency or to disorders of absorption or kidney function. Different hypotheses concerning the etiology have been advanced. From extensive investigations of a case with this disease ALBRIGHT, BUTLER and BLOOMBERG have concluded that the cause is an intrinsic resistance to the effectiveness of vitamin D. FANCONI and GIRARDET, on the other hand, considered the skeletal changes to be secondary to the high urinary excretion of phosphate and therefore suggested the name "Phosphate Diabetes".

Although treatment with vitamin D cannot always completely cure the disease, there is considerable improvement in the skeletal changes following the administration of massive doses. The metabolic changes induced by such a treatment have been subjected to several investigations. FREEMAN & DUNSKY and FANCONI & GIRARDET have found that massive doses of vitamin D, in addition to increasing the calcium absorption, also augment the renal tubular reabsorption of phosphate, thus increasing the capacity of mineralization by two different actions. This hypothesis does not, however, find support from investigations by ROBINSON and NELSON. ALBRIGHT &

SULKOWITCH have stated that the primary actions of vitamin D therapy is to increase the intestinal absorption of calcium and decrease the renal tubular reabsorption of phosphate. All other metabolic changes are considered to be secondary.

Thus, there is disagreement not only concerning the etiology of the disease but also regarding the action of vitamin D when improvement occurs.

ALBRIGHT & REIFENSTEIN and KLEIN & GOW have pointed out the danger of interpreting the metabolic changes during treatment because of the interaction of different processes. The changes observed are not only the sequence of vitamin D action but also the result of changing parathyroid function. Misleading conclusions regarding the mode of action of vitamin D might be made, especially when the studies are not done with great accuracy.

In this paper, the results of metabolic studies performed during the treatment of two previously reported cases of primary vitamin D refractory rickets (WINBERG, BERGSTRAND, ENGFELDT and ZETTERSTRÖM) will be communicated. The manner in which therapy was controlled and the mode of action of vitamin D will be discussed with reference to the results obtained.

Methods

General technique.—Metabolic studies in humans are associated with great technical difficulties because of the impossibility of attaining fully standardized experimental conditions (cf. REIFENSTEIN, ALBRIGHT and WELLS). In balance studies, the error of the method is 10–20 per cent, thus conclusions from such studies cannot be drawn unless the changes are quite significant. Each metabolic period must also be long enough to counterbalance daily variations, and the number of periods must be sufficient when after changing of the experimental conditions the results are then evaluated.

Calcium–phosphate balance has been studied according to the technique employed by REIFENSTEIN, ALBRIGHT and WELLS. The children were given a diet low in calcium and phosphate which has been supplemented with calcium phosphate in substance. Usually the daily intake was 2 g of calcium and 2 g of phosphorus, thus Ca:P ratio has been optimal. In a few periods the calcium and phosphate intake was low, the daily supply of calcium being 0.1 g and that of phosphorus 0.9 g. Vitamin D in oil was administered, perorally, in different dosages, crystalline vitamin D_2 was usually given. In some periods, however, vitamin O_3 was used.

With few exceptions each metabolic period lasted for six days. Urine and feces were collected quantitatively, and the balance for calcium and phosphate was then calculated for the whole period.

Blood samples were drawn by venous puncture and were analyzed as soon as possible. Hemolytic samples were discarded. Double determinations were performed. Calcium and phosphate clearance were calculated from the mean urinary excretion per day during each period, as well as the mean serum level of two or three determinations during this period. The calcium clearance will be given for "non-protein-bound" calcium. The value was determined from the chart devised by MCLEAN and HASTINGS.

Analytical methods.—Feces was dried by combustion in an oven at 500–600° C.

Phosphate in the urine and feces was determined according to FISKE and SUBBAROW, and in blood serum according to YOUNGBERG and YOUNGBERG. Calcium was determined in feces and urine by the method of KRAMER and TISDALL; in blood serum, by the method of BIERING. Alkaline phosphatase in blood serum was determined according to BUSCH and BUSCH. With this method the upper normal limit before puberty is about 16 units per ml. serum.

Results

Metabolic Studies before Therapy was Started

Phosphate metabolism.—As shown in Figs. 1 and 2, there was occasional hypophosphatemia. The serum phosphate level was, however, very labile in both cases. The values given are considerably higher than those observed earlier when the patients were under control (cf. Paper I). This might be the consequence of increased phosphate absorption due to high intake during the metabolic studies (cf. BENJAMIN & HESS and GUNTHER et al.). As was shown from the charts given in Paper I, the absorption of phosphate from the gut was satisfactory. However, the bulk of the phosphate absorbed was excreted in the urine despite the low serum level. This phenomenon cannot be due solely to a primary defect in the kidney tubules, since a considerably reduced daily absorption of phosphate (Periods 5 and 6) caused a highly reduced urinary excretion of phosphate, without change in the serum phosphate level; consequently, there was a considerable fall in phosphate clearance. The values obtained during these experimental conditions are well below those found by DEAN and MCCANCE in adults. Thus, there is, despite the high urinary excretion of phosphate usually found, a good ability to economize phosphate, and phosphate deficiency in the soft tissues might be prevented.

Calcium metabolism.—There were considerable variations in serum calcium concentration, the level occasionally being normal, sometimes decreased (cf. Figs. 3 and 4.). The absorption of calcium from the gut was very low in both cases. In agreement with earlier investigations (for relevant references cf. ALBRIGHT and REIFENSTEIN), the urinary excretion of calcium was found to be extremely low (in Case 1, 10–15 mg per day; in Case 2, 15–20 mg per day). Since the serum calcium level is within normal ranges the calcium clearance is markedly decreased. The low values might be due to an increased tubular Tm for calcium caused by overactivity of the parathyroid glands (cf. TALBOT et al.), which is observed both in ordinary and in refractory rickets (ALBRIGHT, BUTLER and BLOOMBERG; HIGHMAN and HAMILTON).

Initial Metabolic Changes after Treatment with Vitamin D

When therapy was started the patients had not received vitamin D for at least 4–6 months. As was shown in the preceeding paper, the therapy was

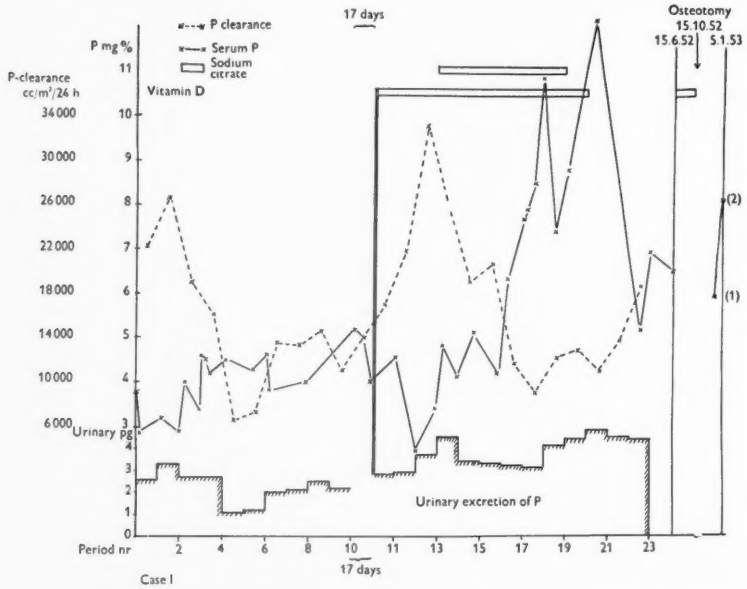

Fig. 1. *Case 1. Serum phosphate level, phosphate excretion in urine and phosphate clearance.*— The serum level was very labile throughout the whole period of observation. Prior to the onset of therapy, the values were mostly slightly hypophosphatemic. A considerably reduced ingestion of phosphate in Periods 5 and 6, caused an immediate fall in urinary excretion and a considerable decrease in clearance. Immediate effects of the administration of vitamin D were a fall in serum concentration, a slightly augmented urinary excretion and, consequently, a considerable increase in clearance. With continued treatment, a marked hyperphosphatemia developed and clearance decreased. Cessation of treatment promted a rapid fall in serum phosphate concentration. Osteotomies were performed in the middle of October 1952. Three months later, the boy had had no treatment, though both legs were immobilized in gypsona during this period, serum phosphate values were still high. (1) Determined last week in Dec. (2) Two weeks later. Cf. Figs. 3 and 6.

started with relatively small doses of vitamin D, and then progressively increased. Thus, it was possible to register the metabolic changes caused by relatively small doses of vitamin D. This was considered to be of special interest since rickets refractory to vitamin D has been thought to differ from ordinary rickets only with regard of the doses required to cause improvement. If this were true, more physiological doses (periods 11–12 in Case 1, and periods 12–13 in Case 2) would have the same metabolic effect as very low doses in the treatment of ordinary rickets.

Phosphate metabolism.—As is shown in Figs. 1 and 2, the administration of vitamin D causes an immediate fall in the serum phosphate level in both cases. The urinary excretion of phosphate remains, however, fairly

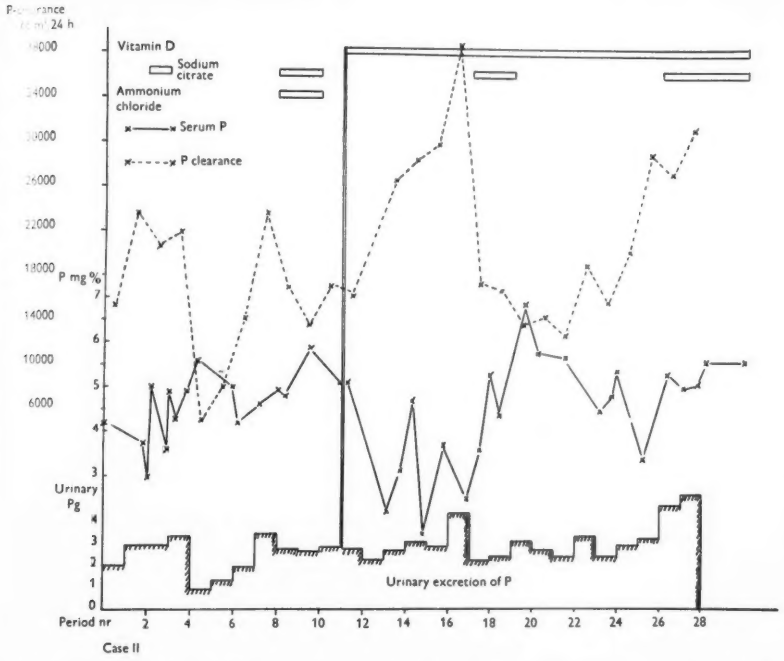

Fig. 2. *Case 2. Serum phosphate concentration, phosphate excretion in urine and phosphate clearance.*—Before treatment, and during the initial stages of treatment with vitamin D, the phosphate metabolism pattern was about the same in this case as in Case 1. However, phosphate clearance after the initial rise and subsequent fall following the administration of vitamin D did not remain at a low level, but increased again as treatment was intensified.

constant. Thus, the phosphate clearance increases considerably, which possibly indicates a diminished renal tubular reabsorption of phosphate. In this stage of therapy, the changes in phosphate metabolism are the same as those found when cases with idiopathic hypoparathyroidism are treated with vitamin D (ALBRIGHT, BLOOMBERG, DRAKE and SULKOWITCH). As shown in Paper I, therapy with vitamin D had no immediate effect upon the retention of phosphate in Case 1. Such an effect was seen in the second period after treatment had been started and was observed at about the same time as there was a maximal effect on phosphate clearance. In Case 2, however, there was no effect on absorption or retention of phosphate despite a marked increase in phosphate clearance, which appeared at about the same time as in Case 1. These findings seem to indicate that vitamin D, directly or indirectly, acts on the renal phosphate excretion and that this effect is not secondary to increased absorption of calcium or phosphate

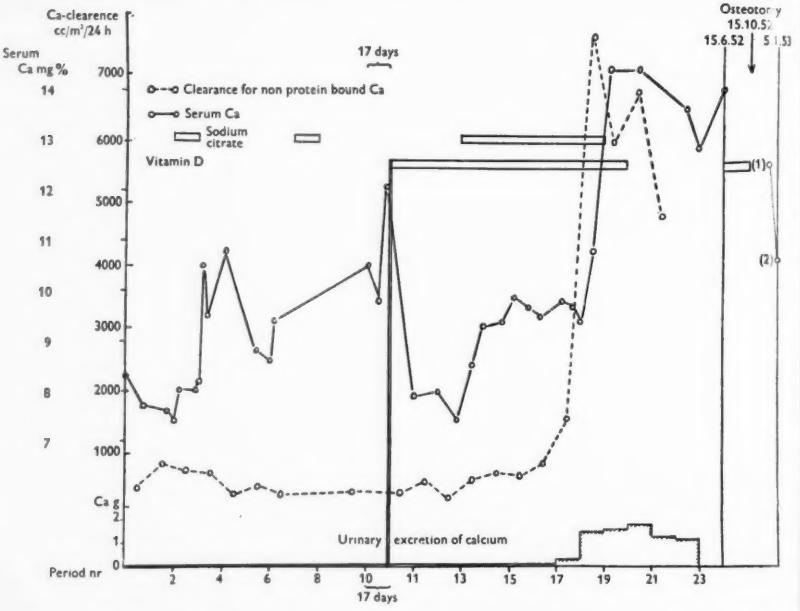

Fig. 3. *Case 1. Serum calcium concentration, calcium excretion in urine and clearance for "non-protein-bound" calcium.*—Before treatment: Considerable variation in serum concentration. Urinary excretion very low, 10–15 mg/day. Clearance very low, unaffected by variations in serum concentrations. Initial effects of treatment with vitamin D: significant drop in serum concentration. Urinary excretion and clearance unchanged. Toxic effects: After 5–6 weeks of treatment (about 16 mill. I. U. of vitamin D given), there was a sudden rise in calcium excretion and calcium clearance. This increase clearly appeared before the rise in serum calcium concentration. Explanation of values (1) and (2) see Fig. 1.

from the gut, which is in agreement with the statements of ALBRIGHT & SULKOWITCH.

Calcium metabolism.—After therapy had been started there was, in both cases, a significant fall in the serum calcium level, as is shown in Figs. 3 and 4. Thus the changes are the same as those found in incomplete healing of ordinary rickets. In Case 1, there was an increase in calcium absorption from the gut, though this effect was preceded by a decrease in the serum calcium level. The decrease in serum calcium concentration was noticed in Period 11; the increased absorption in Period 12. The hypocalcemia then remained until Period 14, despite the high calcium absorption. In Case 2, there was no significant increase in the calcium absorption during the period of observation. In both cases, the clearance for non-protein-bound calcium remained unchanged during these initial periods of treatment.

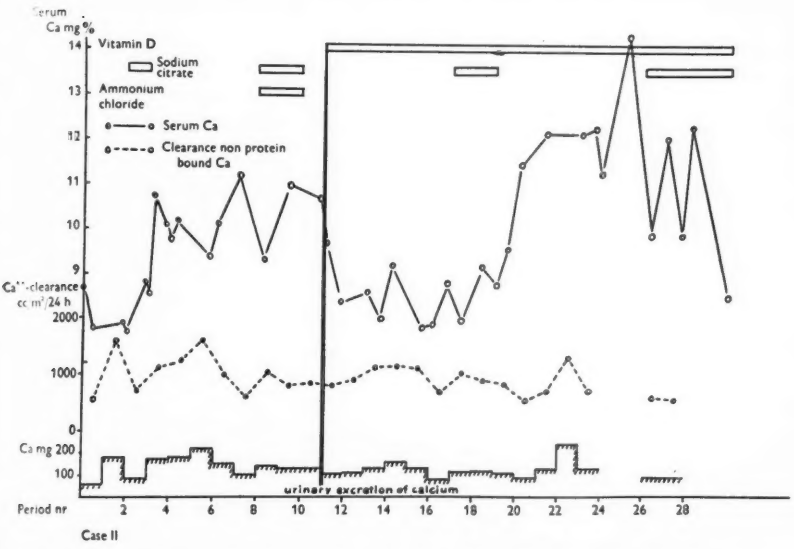

Fig. 4. *Case 2. Serum calcium concentration, urinary calcium excretion and clearance for "non-protein-bound" calcium.*—The pretreatment pattern of calcium metabolism and the changes during the initial stages of treatment were in this case (that did not heal during the metabolic studies) the same as in Case 1. Extremely high doses of vitamin D (3–5 mill. I. U. per day) caused a slight hypercalcemia, but no increase in the urinary excretion of calcium was observed which seemed to be relatively independent of serum calcium concentration. During the Periods 25 and 26 daily Sulkowitch tests were negative.

Metabolic Changes with Continued Treatment

When larger doses of vitamin D were given, characteristic metabolic changes occurred. The results of the studies were most significant in Case 1, since in this case the results of treatment were more rapid than in Case 2.

Phosphate metabolism.—As can be seen from Figs. 1 and 2, the serum phosphate level increased in both cases after the initial fall; in Case 1, a marked hyperphosphatemia developed. In spite of this rise in serum concentration, the urinary excretion was only slightly increased. Thus, there was, in both cases, a marked fall in phosphate clearance after the first periods of therapy where an opposite effect had been noticed. If the glomerular filtration rate is unchanged, these findings indicate that the renal tubular reabsorption of phosphate, which in the first periods of therapy was below the pretreatment value, later had increased. These events might explain the controversial statements concerning the action of vitamin D on the phosphate Tm. HARRISON and HARRISON have claimed that an important factor in the antirachitic action of vitamin D is its ability to

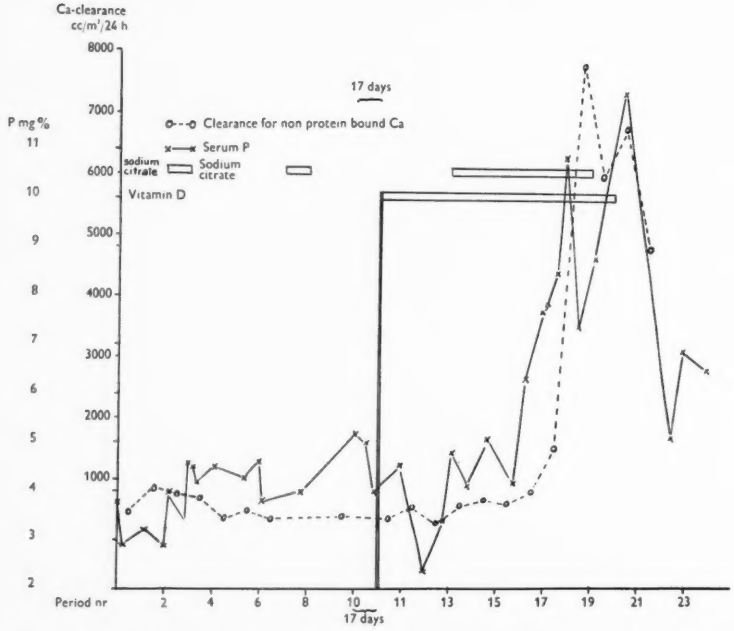

Fig. 5. *Case 1. Serum phosphate concentration and clearance of "non-protein-bound" calcium.* —It is clearly shown that the enormous increase in "non-protein-bound" calcium clearance was preceded by a rise in serum phosphate concentration.

increase phosphate Tm, whereas ALBRIGHT and SULKOWITCH found that vitamin D augments the urinary excretion of phosphate. Our results seem to confirm the suggestions of ALBRIGHT and REIFENSTEIN that the increased phosphate Tm, observed after administration of vitamin D, is secondary to changes in serum calcium and phosphate level and not due to a primary action on renal tubular function.

In Case 1, a high retention of phosphate continued. In Case 2, however, where the same changes in the serum calcium and phosphate and of the phosphate clearance (as in Case 1) were found, there was no significant effect on the retention of phosphate. Thus, the altered renal regulation of phosphate metabolism which vitamin D induces does not presuppose an increased mineralization of the skeleton.

Calcium metabolism.—As is shown in Figs. 3 and 4, there was, after the initial state of hypocalcemia, an increase in the serum calcium level, though the calcium clearance remained unchanged. In Case 1, the calcium balance became strongly positive (Fig. 6), just as for phosphate. In Case 2, there were no highly significant changes of the retention of calcium (Fig. 7).

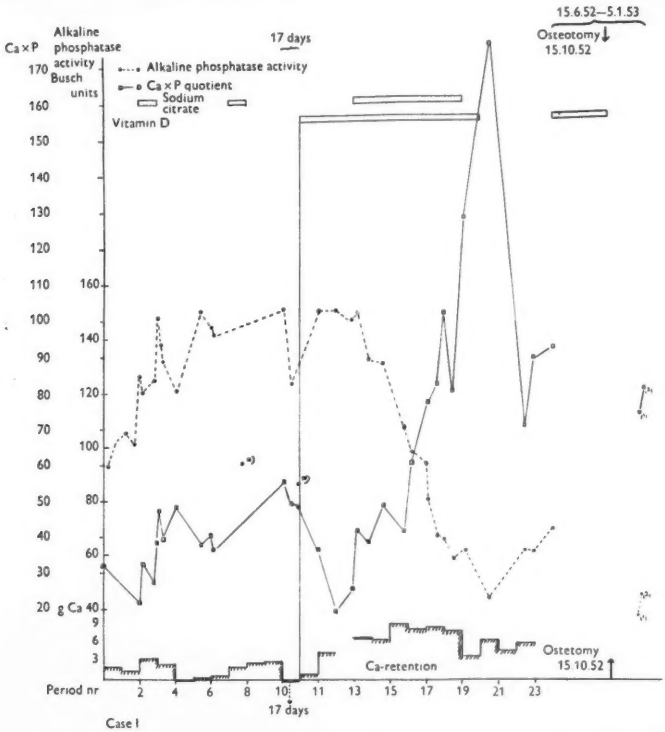

Fig. 6. *Case 1. Alkaline phosphatase activity, Ca × P quotient and calcium retention.*—The pretreatment values for alkaline phosphatase activity were extremely high. When retention of calcium increased, there was a gradual fall in phosphatase activity to moderately low levels, these values tending to rise as soon as treatment was stopped. The Ca × P quotient was still low when there was a definite rise in calcium retention.

Toxic Effects of Vitamin D

Calcium and phosphate metabolism.—Doses which are highly toxic in normal individuals have no deleterious effects in resistent rickets. In Case 2, such extremely high doses as 3–5 millions I. U. per day for more than one month did not cause other abnormal changes than a hypercalcemia. The urinary output of calcium remained very low, however, (Fig. 4).

In Case 1, the level of toxicity was earlier exceeded. As a sequal to toxic reactions the serum phosphate concentration rose considerably, the urinary output of calcium increased rapidly to very high values and a pronounced hypercalcemia developed. Hypercalcuria was considered the most characteristic feature. The amount of calcium excreted in the urine had remained unchanged during several periods of treatment. In Period 18 (Fig. 3), a

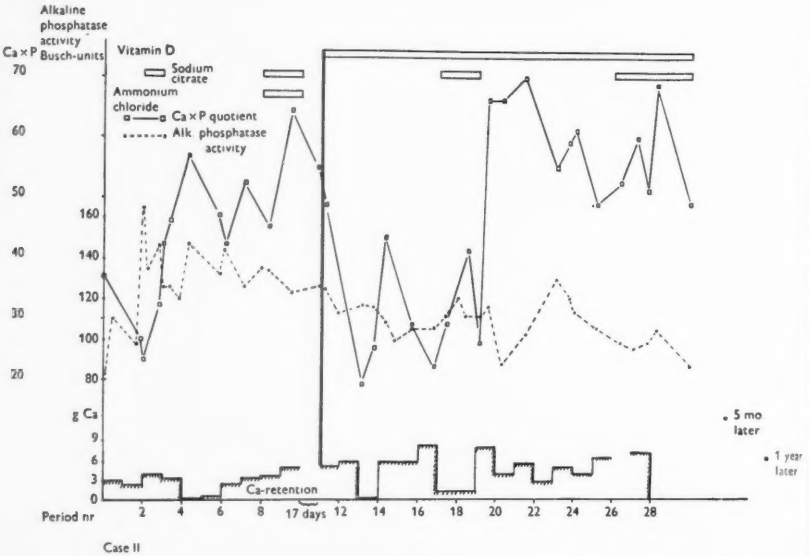

Fig. 7. *Case 2. Alkaline phosphatase activity, Ca × P quotient and calcium retention.* Alkaline phosphatase activity was extremely high before treatment. During the last metabolic periods there was a progressive but slight decrease in this activity. During these last periods there was also a tendency to increased calcium retention. Signs of healing appeared in spite of a fairly high phosphate clearance.

rise in the calcium clearance took place, and in the next period the clearance increased to a value enormously high when compared to earlier ones. This elevation seemed to preceed the increase in calcium concentration in the serum. In Period 18 there were 9.6 mg calcium per 100 ml and in the next period 9.4 and 10.7; the values thus being within the normal range. In Periods 20–23, however, there was a marked hypercalcemia, though the calcium clearance was decreasing. Thus, high urinary output of calcium as occurs in vitamin D intoxication cannot be solely the result of exceeding the renal treshold. Instead, there seems to be some association between the serum phosphate level and the urinary excretion of calcium, since the high calcium clearance was noticed when the serum phosphate level was extremely high (Fig. 5). Furtheron, in Case 2, where no rise in the serum phosphate concentration took place, no hypercalcuria developed. (Figs. 2 and 4). Hypercalcuria as well as hyperphosphatemia might be the result of kidney damage.

When the treatment was discontinued the phosphate clearance increased and there was a rapid fall in the serum phosphate concentration (Fig. 1).

TABLE 1

Case 1. Effect of treatment on intravenously injected phosphate. Serum values and urinary excretion of phosphate.

Before treatment the patient was given 310 mg P (as Na_2HPO_4), intravenously. When healed he was given 155 mg P. Serum values decreased much more slowly after healing than before.

Time i min. after injection of phosphate	Serum phosphate		Urinary excretion of phosphate in mg per minute	
	Before treatment	After treatment	Before treatment	After treatment
0	4.2	4.0		
15	14.3	12.8	8.4	1.4
30	10.5	11.3	4.6	0.8
45	6.6	10.5	5.0	2.0
70	6.7	10.2	3.0	1.6
90	6.1	—	1.8	—
120	6.0	9.1	1.2	1.4
145		8.8		0.9

The serum calcium level remained at about the same high level for one month but the urinary output of calcium diminished (Fig. 3).

Effect of Treatment on Intravenously Injected Phosphate

In Case 1, the metabolism of intravenously injected phosphate was studied. As can be seen from Table 1, there was, immediately after the injection of phosphate, a rapid rise in the serum phosphate level. The concentration then fell, the decrease being much more rapid before treatment than after. In both instances the injected phosphate was quantitatively excreted in the urine. After treatment, the excretion was slower, thus there was, as is seen in Table 2, a considerable decrease in the exogenous phosphate clearance, which is in agreement with the findings of FREEMAN and DUNSKY. Neither before nor after treatment could intravenously injected phosphate be utilized for mineralization. In both experiments the phosphate injected was labelled. No other conclusions could be made than that only minute amounts of the phosphate injected were excreted in the feces.

Estimation of the Course of Mineralization

Increased mineralization of the skeleton should be determinable as soon as possible in order to permit a satisfactory control of therapy. X-ray examination of the skeleton is too rough a method to give accurate information. The retention of calcium and phosphate reflects the deposition of

TABLE 2

Case 1. Effect of treatment on intravenously injected phosphate. Exogenous phosphate clearance.

Calculation of the clearance of exogenous phosphate was made according to FREEMAN and DUNSKY. Clearance for exogenous phosphate was considerably reduced after healing.

	Amount of phosphate administered	Total excretion of phosphate in 2 hours	Exogenous phosphate clearance/min.	
			First half-hour	Second half-hour
Before treatment . . .	310 mg	414 mg	44 ml	48 ml
After treatment	155 »	170 »	5.7 »	13.3 »

mineral salts in the skeleton. This method is, however, associated with too great technical difficulties to be used as a routine method; i.e., because of the long periods during which the balance must be studied.

A rise in the serum level of calcium and phosphate takes place some time after therapy has been started. The concentration of these ions in serum does not, however, reflect the intensity of the mineralization process accurately. In both of our cases, hypercalcemia developed. In Case 1, there was a considerable increase in calcium retention before hypercalcemia was noticed. On the contrary, in Case 2, there was hypercalcemia without any increase in the retention. Roughly the intensity of the mineralization process has been found to be proportional to the serum phosphate level. The serum phosphate concentration is, however, too labile to permit exact conclusions. SHIPLEY, KRAMER and HOWLAND have claimed that the Ca × P quotient in serum must be raised to values of about 35–40 for inducement of mineral deposition. However, Fig. 6 shows that there is a decrease in the quotient when there (in Case 1) was an increase in the retention of calcium. In Case 2, however, the calcium retention was unchanged when the Ca × P quotient had been 50–70 for almost one month (Fig. 7). These findings support the opinion that the Ca × P quotient is not the only measure of mineral deposition and consequently it is not a proper method for evaluating therapy.

As is shown in Fig. 6, the alkaline phosphatase activity in serum is enormously elevated before treatment. When the retention of calcium rises, there is a decrease of alkaline phosphatase activity in the serum, which continues as long as vitamin D is administered. By omission of therapy there is again a rise. As is shown in Fig. 7, (in Case 2) not until the last metabolic periods was there a slight drop in alkaline phosphatase activity. During this time there was also a tendency to increased calcium retention.

These signs of healing appeared in spite of a fairly high phosphate clearance. The improvement then continued as judged from measurements of alkaline phosphatase activity and X-ray examinations. These findings suggest that the alkaline phosphatase activity in blood serum most closely follows the degree of mineralization in the skeleton, which is in agreement with the findings of MORRIS, STEVENSON, PEDEN and SMALL. A careful control of alkaline phosphatase activity seems to be the best way to evaluate the results of therapy.

Comment

The clinical features of rickets refractory to vitamin D are in some ways different from those observed in ordinary rickets. Thus, in the ordinary type of rickets the disease is not only limited to the skeleton but more generalized and the children are more seriously ill. In the metabolic investigations it has not, however, been possible to demonstrate any significant differences. The studies of phosphate metabolism do not yield evidence for the existance of a primary defect in the renal tubular reabsorption of phosphate. Quite recently, RUPP and SWOBODA have arrived at the same conclusions. The massive doses of vitamin D administered to the children with vitamin D refractory rickets have given roughly the same metabolic changes as those observed when ordinary rickets is treated with more physiological doses except that there is an initial fall in the serum phosphate level. There is in these cases some defect in the physiological processes regulating mineralization. The nature of this defect remains obscure. Nothing in the results reported in this paper speaks against the statement originally made by ALBRIGHT, BUTLER and BLOOMBERG, that this type of rickets is due to an intrinsic resistance to the effectiveness of vitamin D therapy. The cause of this resistance, however, remains obscure.

From studies of the calcium and phosphate metabolism in vitamin D refractory rickets and in idiopathic hypoparathyroidism, ALBRIGHT and SULKOWITCH have raised the hypothesis that vitamin D not only augments the calcium absorption from the alimentary tract, but also reduces the renal tubular reabsorption of phosphate. This later effect of vitamin D remains curious in view of the observations of HARRISON and HARRISON, that vitamin D in rachitic dogs increases markedly the maximal rate of reabsorption of phosphate by the kidney tubules. In normal experimental animals, however, the effect on phosphate reabsorption was much less pronounced. Therefore, ALBRIGHT and REIFENSTEIN suggested that the results obtained by HARRISON and HARRISON in the rachitic animals was not due to a primary action of vitamin D but to an inhibiton of the hormone secretion from the parathyroid glands due to an elevation of the calcium

concentration caused by vitamin D. The results reported in this paper give further evidence for this hypothesis. In both cases, vitamin D caused the same changes of the phosphate clearance as those found by ALBRIGHT and SULKOWITCH, after administration of vitamin D to patients with hypoparathyroidism. That such an effect was observed might be due to the fact that the calcium level in serum decreased, thus, the activity of the parathyroid glands was not depressed. When the serum calcium level became normalized the phosphate clearance decreased.

Due to the interrelationship of many factors, such as the equilibrium between the mineral salts in the skeleton and bone salt producing ions in the blood serum, and the interaction of vitamin D and the secretion of parathyroid hormone, it is impossible to interpret all the metabolic changes observed after the administration of vitamin D. The findings concerning the mode of action of vitamin D in refractory rickets can be summarized as follows: In the first stages, after the administration of vitamin D, there is an increased urinary excretion of phosphate which causes a decrease in the serum phosphate level; at the same time, a hypocalcemia develops. Since the effect on phosphate metabolism is also seen in hypoparathyroid states, this action of vitamin D cannot be caused by some interrelationship with parathyroid hormone secretion. The hypocalcemia, however, might be due to a decrease in the activity in the parathyroid glands if it is believed, as do KLEIN and GOW, that vitamin D directly or indirectly inhibits the secretion of parathyroid hormone. Increased mineralization (in Case 1, indicated by a significant increase in the calcium retention) is started despite an initially low $Ca \times P$ quotient. This phenomenon might be due to a direct effect of vitamin D on the bone tissue. This conclusion presupposes, however, that the increased mineralization is not due solely to ceased bone resorption caused by an inhibition of the secretion from the parathyroid glands. That vitamin D also exerts an effect on calcium absorption from the alimentary tract is most clearly demonstrated by the fact that hypercalcemia develops despite a continued mineralization.

It can hardly be assumed that vitamin D alone exerts so many different actions as has been summarized above. Beside the effects observed in our studies, other metabolic changes have been noticed. It is a well-known fact that vitamin D, in cases with rickets, causes an increased urinary excretion of citrate (FREUDENBERG; HARRISON and HARRISON) which might be due to an increased accumulation of citrate (BELLIN, HERTING, CRAMER, PILEGGI and STEENBOCK). This effect demonstrates that the vitamin has some general metabolic action. It might be supposed that an effect of this type on cell metabolism is the primary action and that other changes observed are secondary.

Summary

Studies of calcium and phosphate metabolism have been performed in two cases of primary vitamin D refractory rickets. The metabolic changes were found to be roughly the same as in vitamin deficiency rickets. The administration of vitamin D causes increased intestinal absorption of calcium and phosphate, increased urinary excretion of calcium and phosphate and a normal or elevated serum phosphate level, during healing. Concerning the action of vitamin D, the results suggest that there is in the initial stages of therapy a direct or indirect action on the kidneys, causing phosphate excretion. Furthermore, there is evidence of a more direct action of vitamin D on the bone tissue, causing deposition of mineral salts. The effect on the skeleton is either caused by a primary action on osseous tissues, or by an inhibition of the hormone secretion from the parathyroid glands, which is not secondary to changes in the serum calcium or phosphate levels.

In vitamin D intoxication, hypercalcuria might preceed the hypercalcemia, and therefore, hypercalcuria cannot be due solely to an exceeding of the renal treshold. The urinary excretion of calcium must be controlled to prevent the development of toxic reactions. The Ca × P quotient is shown not to be a relevant regulator of the intensity of mineralization. The most accurate information concerning the intensity of mineralization of the skeleton during treatment seems to be obtained by the alkaline phosphatase activity in the blood serum.

Le metabolisme du calcium et du phosphate dans le rachitisme primaire résistant à la vitamine D.

Le metabolisme du calcium et du phosphate a été étudié dans deux cas de rachitisme primaire résistant à la vitamine D. On a trouvé à peu près les mêmes changements du métabolisme que dans le rachitisme par déficience vitaminique. L'administration de vitamine D provoque une augmentation de l'absorption intestinale du calcium et du phosphate ainsi que de l'ecxrétion urinaire du calcium et du phosphate et donne un taux normal ou élevé de phosphate sérique pendant la guérison. En ce qui concerne l'action de la vitamine D on pense, d'après les résultats, qu'il y a dans les premiers stades du traitement une action directe ou indirecte sur les reins, donnant une excrétion de phosphate. Il semble, de plus, qu'il y ait une action plus directe de la vitamine D sur le tissu osseux, qui provoquerait un dépôt de sels minéraux. L'effet sur le squelette est occasionné par une action primaire sur les tissus osseux ou par une inhibition de la sécrétion hormonale des glandes parathyroïdes, qui n'est pas secondaire aux changements des taux du calcium ou du phosphate dans le sérum. On montre que le quotient Ca × P n'est pas un régulateur influençant l'intensité de la minéralisation. Dans l'intoxication par la vitamine D l'hypercalciurie peut précéder l'hypercalcémie; l'hypercalciurie ne peut donc pas être uniquement occasionnée par un dépassement du seuil rénal. L'excrétion urinaire du calcium doit être controlée pour empêcher que des réactions toxiques ne se développent. Il semble que le renseignement le plus exact concernant l'intensité de la minéralisation du squelette pendant le traitement soit l'activité de la phosphatase alcaline dans le sérum sanguin.

Calcium- und Phosphat-Stoffwechsel in primäre, vitamin D-resistente Rachitis.

In zwei Fällen von primärer, vitamin D-resistenter Rachitis wurden Untersuchungen über den Calcium- und Phosphat-Stoffwechsel ausgeführt. Es zeigte sich, dass die Stoffwechselstörungen weitgehend die gleichen sind wie bei Vitaminmangel-Rachitis.

Die Verabreichung von Vit. D bewirkt eine gesteigerte Resorption von Calcium und Phosphaten aus dem Darm, gesteigerte Ausscheidung beider Komponenten im Urin, und ein normaler oder erhöhter Phosphatspiegel im Serum während der Heilungsphase. Bezüglich der Wirkung des Vit. D deuten die Resultate darauf hin, dass im Initialstadium der Behandlung eine direkte oder indirekte Beeinflussung der Nieren vorliegt, welche zur vermehrten Phosphatausscheidung führt. Ferner besteht eindeutig eine direkte Wirkung des Vitamin D auf das Knochengewebe, welche zur Einlagerung von Mineralsalzen führt. Die Wirkung auf das Skelett ist entweder durch eine primäre Beeinflussung des Knochengewebes, oder durch eine Hemmung der Hormonproduktion in den Nebenschilddrüsen bedingt. Letztere wird nicht etwa sekundär, durch die Veränderungen des Serumkalk- oder Phosphatspiegels bedingt. Bei der Vit. D-Vergiftung kann die Hypercalcurie vor der Hypercalcaemie auftreten, was darauf hinweist, dass die Hypercalcurie nicht allein durch ein überschreiten der Nierenschwelle bedingt sein kann. Die Kalkausscheidung im Urin muss kontrolliert werden, um das Auftreten toxischer Reaktionen zu vermeiden. Der Quotient Ca × P kann nicht als massgebender Regulator für die Intensität der Mineralisation betrachtet werden. Die zuverlässigste Orientierung über die Mineralisationsvorgänge im Skelett während der Behandlung ergibt offensichtlich die Bestimmung der alkalischen Phosphatase im Blutserum.

Dos casos de raquitismo primario refractario a la vitamina D, respecto al metabolismo del calcio y del fósforo.

Se han efectuado estudios en dos casos de raquitismo primario refractario a la vitamina D, respecto al metabolismo del calcio y del fósforo. El intercambio metabólico hallado fué aproximadamente el mismo que en los raquitismos por deficiencia de vitamina D. Con todo, como fué destacado en un artículo previo, otros signos clínicos sugieren una patogenia diferente entre el raquitismo refractario y el raquitismo por deficiencia. La administración de vitamina D produce un aumento de absorción intestinal del calcio y fósforo, aumento de la excreción urinaria de calcio y fósforo, y un nivel normal o elevado del fosfata sérico durante la curación. En lo concerniente a la acción de la vitamina D, los resultados sugieren que hay, en las etapas iniciales del tratamiento, una acción directa o indirecta de los riñones en la determinación de la excreción del fosfato. Con todo, es evidente una acción mas directa de la vitamina D en el tejido óseo, que produce un depósito de las sales minerales. El efecto sobre el esqueleto es producido, sea por una acción primaria sobre el tejido óseo, o por inhibición de la hormona paratiroidea no secundaria a los cambios en el nivel sérico del calcio y fósforo. El coeficiente Ca × P no se presenta como un regulador de la intensidad de la mineralización. En la intoxicación por vitamina D, la hipercalciuria puede preceder a la hipercalcemia, no pudiendo por lo tant ser debida únicamente a que la hipercalcemia excedió el umbral renal. La excreción urinaria de calcio debe ser controlada para prevenir el desarrollo de reacciones tóxicas. La mas segura información en lo que concierne a la intensidad de la mineralización del esqueleto durante el tratamiento parece ser la obtenida por la actividad de la fosfatasa alcalina en el suero sanguíneo.

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Studies of the Anemia in Ulcerative Colitis with Special Reference to the Iron Metabolism

by M. BARR, S. DELAVA[1] and R. ZETTERSTRÖM

In chronic ulcerative colitis a pronounced anemia is frequently observed. This anemia might be normochromic or hypochromic. LAGERCRANTZ, in a follow-up examination of 134 cases of ulcerative colitis in childhood, found anemia in almost all cases; in 16 hemoglobin level was less than 7.5 g per 100 ml. According to LAGERCRANTZ, progressive anemia was found to be a sign of poor prognosis as well as a spreading of the pathological changes over the entire colon or the appearance of liver disease. Absence of severe anemia was a favorable sign. An improvement of the general state of patients with ulcerative colitis when they recover from the anemia after blood transfusions has been reported (RACHWALSKY, LAGERCRANTZ).

Since the anemia associated with ulcerative colitis has not been sufficiently studied for proper classification, it is difficult to conclude whether the anemia is caused solely by blood loss from the bowel, or if there are additional factors responsible for its development. Some of the features of the anemia are those of an iron-deficiency anemia. Furthermore, oral treatment with iron in fairly large doses and over a lenghty period has been reported to induce improvement of the anemia (LAGERCRANTZ). Thus, there is in many cases the same favorable response to iron therapy as in the uncomplicated anemia of chronic bleeding. However, the intensity of bleedings and the distribution and extent of the pathological changes in the bowel is not always proportionate to the degree of the anemia (POLLARD). This might indicate that there is, in addition to an iron-deficiency, an impairment of erythropoiesis and iron metabolism. This disturbance might be of the same type as that seen in the anemia of infection and in some other chronic diseases (for relevant references cf. CARTWRIGHT & WINTROBE, 1952).

Since anemia is one of the most outstanding symptoms in ulcerative colitis, and since the cause of its development is not quite clear, the studies

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TABLE 1

Clinical data of nine patients with ulcerative colitis.

Group I indicates that the process according to the X-ray examination involved only the distal part of the colon. When the changes are classified as Group II the process was found in most parts of the colon. When the changes were found in the entire colon and in some instances also in the lowest part of the ileum the X-ray findings were termed Group III.

Patient	Age in years	Sex	Weight in kg	Duration of disease in years	Severity of disease, according to general condition	X-ray of colon, group	Bleeding from the bowel	Remarks
A. U.	14	F	34	1½	+ + +	III	+ +	
M. P.	14	M	39	2½	+	II	+	Complicated by infectious hepatitis
N. B.	11	F	29	3	+ + +	III	+ +	Pronounced psycholability
L. L.	10	M	27	4	+ + +	III	+ + +	Pronounced psycholability
H. B.	15	F	42	8½	+ +	I	+ + +	May have been periarteritis nodosa
G. S.	13	F	49	3	+ +	II	+	
A. E.	6	F	25	3	+ + +	III	+ +	When investigated was in remission after chicken pox
W. C.	6	M	22	1½	+ +	II	+ +	
B. N.	16	F	36	9	+ + +	III	+ +	Pronounced retardation of sexual maturation

to be reported herein have been performed. The use of radioactive iron and the determinations of serum iron and iron-transporting protein has provided the means of investigating more accurately the cause of the anemia.

Material

The studies were performed in 9 children with ulcerative colitis. The age of the patients ranged between 6 and 16 years. In most of the cases the disease had become chronic and in only 3 of the patients the duration of the disease was less than one year. The course of the disease had, in all cases, been typical of ulcerative colitis and there were also typical findings on rectoscopy and roentgen examination of the colon. In some of the patients with disease of long duration, there was delayed growth and retarded sexual development. The main clinical data are summarized in Table 1.

The serum protein level was slightly reduced in patients with severe symptoms. Electrophoretic patterns (micro-electrophoresis, Antweiler) showed slight increase in the α_2-globulin fraction (range, 0.4–0.9 g per 100 ml; mean, 0.7 g per 100 ml) and

usually a marked increase of the γ-globulin fraction (range 1.3–2.1 g per 100 ml; mean, 1.8 g per 100 ml, or 27 per cent of the total serum protein) at the expense of albumin (range, 2.5–4.0 g per 100 ml; mean, 3.4 g per 100 ml, or 51 per cent of the total serum protein).

Methods

Test of the utilization of oral iron.—This test was performed with iron labelled with the isotop Fe^{59}. To a ferrous pyrophosphate mixture containing 25 mg Fe^{++}, which was used as carrier, 2.5 μ C of Fe^{59} (1 μ C per 5–20 μg), supplied by A. E. R. E., Harwell, as ferric chloride, was added. Since the ferrous mixture used will reduce small quantities of ferric iron, it can be assumed that all of the radioactive iron given to the subjects was in the ferrous state. The solution was given to the patients at 7 a.m. after they had been fasting overnight. The subjects were allowed nothing to eat for 3 hours after the dose was administered. After the administration of Fe^{59}, feces was collected quantitatively, for 3 days. Blood samples were taken on the 6th and 16th days.

Measurement of radioactivity in the samples:—

Feces. The total amount of collected feces from each patient was homogenized with water with aid of a warring blender. The total volume of the feces mixture was measured (about 2–3 l), and two aliquots (10–15 ml) for double determinations were taken for measurement of the radioactivity. The samples were desiccated by combustion with sulfuric acid and hydrogen peroxide. The ignited samples were made up to a suitable volume, and the radioactivity was determined according to a method described by AGNER, BONNICHSEN & HEVESY. The method used is based upon the principle that 500 μg iron is precipitated as ferrous sulphide, the precipitate then being plated. The countings were made with a thin mica end-window Geiger-Müller tube. If there was poor correlation between the double determinations the analytical procedure was repeated.

Blood. The blood was hemolysed with the aid of a few drops of concentrated aqueous ammonia. A suitable amount of blood was then ignited and the amount of radioactivity was measured in the same way as in the feces samples.

Standards. An aliquot of the original radioactive solution was used as a standard. During the diluting procedures, ferrous sulphate was added as a carrier and the solution was acidified with sulphuric acid to a pH of about 1 to prevent precipitation of the iron and subsequent adherence to the glass. The iron was then precipitated as ferrous sulphide, as in the biological samples.

Calculation of the utilization.—The percentage absorption of the oral dose of iron was calculated from the amount of radioactivity found in the feces. For estimating the percentage radioactivity utilized for hemoglobin synthesis, the total circulating hemoglobin was measured with the CO-method described by SJÖSTRAND, as modified for children by KARLBERG & LIND.

Other analytical methods.—For the determination of the hemoglobin level a photometric colorimeter was used. The photometer had been standardized against the oxygen capacity (the factor 1.36 was applied). Serum iron was determined according to the method of VAHLQUIST. The total iron-binding capacity of serum (transferrin according to HOLMBERG & LAURELL, or siderophilin according to SCHADE, REINHART & LEVY) was determined by the method of RATH & FINCH.

TABLE 2

Hematologic observations on admission in the patients with ulcerative colitis.

Patient	Hemoglobin g per 100 ml	Red cells millions per c.mm	MCHb micro-microg.	Reticulocytes per cent	Mean cell diameter according to Price-Jones μ	White cells per c.mm	Leucocytes per cent	Serum iron mi-crog per 100 ml	Bleeding from the bowel	Treatment after admission
A.U.	9.8	4.0	24	0.8	5.8	6,900	57	29	+	—
M.P.	12.1	4.0	30	1.4	7.4	9,800	55	67	+ +	—
N.B.	11.3	3.9	29	1.6	7.1	4,600	55	10	+	Blood transfusions, 400 ml. Iron i.v., 640 mg
L.L.	12.2	4.0	31	2.2	6.8	15,200	69	34	+ + +	Blood transfusions, 250 ml. Iron i.v., 340 mg
H.B.	9.1	2.7	34	5.5	7.0	6,000	65	64	+ +	Blood transfusions, 850 ml
G.S.	10.5	3.5	33	3.7	6.9	7,900	74	24	+ +	Blood transfusions, 700 ml. Iron i.v., 400 mg
A.E.	7.1	2.9	24	1.3	7.5	5,700	62	32	+ +	Blood transfusions, 1000 ml. Iron i.v., 360 mg.
W.C.	11.5	3.8	30	1.7	7.7	7,800	52	34	(+)	—
B.N.	10.3	3.6	31	1.4	7.0	5,000	58	16	+	—

Results

The hematologic data on admission to the hospital are summarized in Table 2. In most of the subjects there was a more or less pronounced anemia. In only two of the patients (A. U. and A. E.), the anemia was hypochromic; in the other subjects it was normochromic in character. In a single case the mean red cell diameter was significantly lowered. The reticulocytes were found to be within the normal range. In all cases there was a marked reduction in the serum iron and in many cases the values were extremely low.

Thus, the anemia in most instances was found to be normochromic, although the serum iron level was highly reduced. This fact might indicate that the anemia is not caused by a simple iron deficiency due to blood loss from the bowel. This suggestion also finds support from the observation that there was not any firm correlation between the degree of anemia and the history of bloody stools. The finding that treatment with blood transfusions and intravenous administration of high doses of saccharated iron oxide (Intrafer) provided only a slight improvement in the anemia is also in harmony with this statement. The ineffectiveness of therapy is clearly demonstrated when the hemoglobin values in Table 2 are compared with those given in Fig. 2 (which shows the values found after the treatment listed in Table 2). Nor was there found any reticulocyte peak after intra-

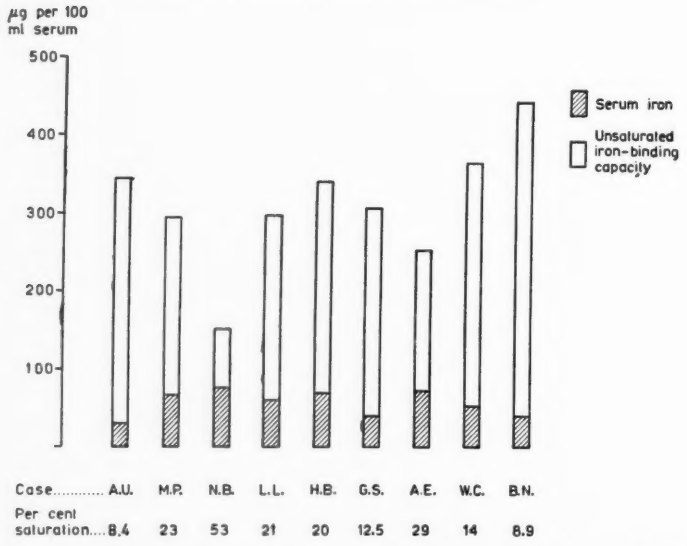
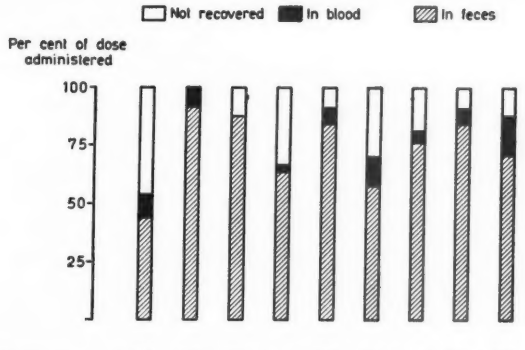


Fig. 1. Serum iron level and iron-binding capacity in patients with ulcerative colitis.

venous iron therapy. Only when the patients went into a remission was there a remarkable improvement of the anemia.

The results of the determination of total ironbinding capacity (TIBC) and of the serum iron level in the children with ulcerative colitis is shown in Fig. 1. All determinations were obtained after the treatment reported in Table 1. It is clearly seen that there were considerable variations in the concentration of iron transporting protein. In some of the patients the values were within the normal range as described by SMITH, SCHULMAN & MORGENTHAU (mean 340), and by HAGBERG, 1953 (mean 353). In most of the cases, however, the values were lower than those found in the normal, and in cases N. B. and A. E. the values were extremely low. Only in one case was the transferrin level found to be considerably higher than in normal children. Despite treatment the serum iron level remained lower than normal (cf. VAHLQUIST, HAGBERG, 1953) in many cases. In one case, this low serum iron level was associated with a high unsaturated iron-binding capacity; the usual finding in true iron deficiency anemia (LAURELL, SMITH et al., HAGBERG, 1953).

In Fig. 2, the results of the studies of iron metabolism by means of radioiron are given. If the high doses of iron administered to each patient (25 mg Fe^{++}) are taken into account, it is clearly demonstrated from this figure that there was a very high absorption of iron from the alimentary tract. DARBY,



Case	A.U.	M.P.	N.B.	L.L.	H.B.	G.S.	A.E.	W.C.	B.N.
Hb. (g %)	9.8	12.1	13.6	11.0	7.5	10.9	10.6	11.5	10.3
Serum iron (μg %)	29	67	70	53	69	39	73	52	40
Per cent of oral dose absorbed	56	8	12	36	15	42	22	15	28
Per cent of absorbed iron utilized for hemoglobin synthesis	18	100	0	7	47	30	21	49	60

Fig. 2. The recovery of an oral dose of 25 mg Fe^{++} labelled with Fe^{59} in patients with ulcerative colitis.

HAHN, STEINKAMP & KASER have found that in normal growing children the absorption may be only 12 per cent at a dietary intake of about 2–5 mg iron. In the subjects with ulcerative colitis the range was found to be 8–56 per cent of the oral dose. The percentage absorption was high even in subjects who had not received specific therapy for their anemia. Also, in some of the children who had been treated with iron, intravenously, and with blood transfusions, the absorption was high, as is demonstrated from the results obtained in the case G. S. No true correlation was found between the amount of iron absorbed and the iron-binding capacity of the serum. In some of the subjects with a low saturation of iron-transporting protein, the absorption of iron was very high (A. U., G. S. and B. N.). In others of the patients, however, the absorption was relatively high, despite a saturation index not markedly below the normal level.

From Fig. 2 it is also seen that there was in most of the patients, a low utilization for hemoglobin-synthesis of the iron absorbed. In only one patient (M. P.) was there maximal utilization; in the other subjects, only a part of the iron appeared in the red cells after 16 days. In the cases A. U., N. B., L. L., and A. E., the rate of incorporation of the absorbed radioiron in hemoglobin was markedly reduced. The slow rate of utilization of the iron absorbed is demonstrated by the fact that DUBACH, MOORE & MINNICH found that in normal subjects from 70 to 90 per cent of the dose of intra-

venously injected radioiron was used for hemoglobin-synthesis within the first six to nine days. Furthermore, BADENOCH & CALLENDER have reported that almost all of the radioiron absorbed was rapidly utilized for hemoglobin-synthesis in subjects with simple hypochromic anemia. Since in our patients with ulcerative colitis there was only small amounts of blood in the feces, or none at all, during the period of study, it can be concluded that the radioactivity which was not recovered was not lost in the feces after the period of fecal collection. As has been found in patients with febrile conditions (DUBACH, CALLENDER & MOORE) there is in ulcerative colitis absorption of iron in excess of what is used for hemoglobin synthesis. It appears fairly definite, therefore, that in ulcerative colitis a primary increased deposition of iron in the iron stores, or a failure of the marrow function, in many cases is the main cause of the anemia.

Comment

The importance of differentiating between a true iron-deficiency anemia and the anemia seen with infections and chronic systemic diseases must be recognized when treating the anemia associated with ulcerative colitis. From the clinical point of view, it is often difficult to determine which type of anemia is present, since the anemia of infection resembles iron-deficiency anemia from several aspects. In two respects there are, however, definite differences between the two. First, the anemia associated with infections, rheumatoid arthritis and other chronic systemic diseases, is refractory to iron therapy (KUHNS, GUBLER, CARTWRIGHT & WINTROBE). The other difference between these types of anemia is that the total iron-binding capacity of the serum is decreaed in the presence of infection and some chronic diseases (cf. CARTWRIGHT & WINTROBE, 1949, HAGBERG 1953), while it is increased in iron-deficiency anemia (LAURELL, SMITH ET AL., HAGBERG, 1953). When both conditions are present in the same individual the total iron-binding capacity is, however, either normal or somewhat decreased (CARTWRIGHT & WINTROBE, 1952).

In the patients with chronic ulcerative colitis studied, the anemia was found to be normochromic, with two exceptions. There was a persistently low serum iron level and often, but not regularly, a decrease in the concentration of the iron-transporting protein in the plasma. The reduction in plasma iron, generally, was greater than the reduction of iron-binding protein, with the result that the per cent saturation of the protein with iron was decreased from 34 per cent (the normal value for the age of patients according to HAGBERG, 1953) to an average of 18 per cent. In most of the patients with ulcerative colitis there was a high absorption of iron from the alimen-

tary tract, which gives evidence that decreased absorption of iron plays no role either in the production of anemia or of the hypoferremia. There were, however, signs of a profound disturbance of iron metabolism as evidenced by the slow rate of iron utilization for hemoglobin-synthesis. The often only slight improvement of anemia and the fact that there was a persistance of the hypoferremia, after blood transfusions and treatment with iron intravenously, seems to be another indication of a disturbance in iron metabolism. Thus, many of the characteristics of the anemia in ulcerative colitis are the same as those found in the anemia of infection and in the anemia of different chronic systemic diseases. In addition, there are also features typical of an iron-deficiency anemia. In some of the cases, the characteristics of an anemia of infection predominated, while in other cases, there were more definite symptoms of an iron-deficiency anemia. During the course of the disease the anemia may change character.

According to the results obtained in this study, the treatment of anemia complicating ulcerative colitis might differ according to the type of anemia which is associated with the primary disease. With ordinary clinical tests it seems, in most cases, to be very difficult to determine if there is an iron deficiency. On the other hand, such a deficiency might be suspected when there is a history of long-standing bleeding from the bowel. In these subjects it can be expected that there will be a response to peroral treatment with iron, since there is a high absorption of iron from the alimentary tract. In patients with poor tolerance to peroral treatment with iron, intravenous administration of colloidal iron preparations might be recommended (cf. Brown, Moore, Rejnafarje & Smith, Hagberg, 1951). It must, however, be pointed out that it cannot be expected that iron therapy will cure the anemia or the hypoferremia. Due to the disturbance of iron metabolism which is associated with ulcerative colitis, as well as with infections, excessive iron therapy, especially when iron is given intravenously, might cause hemosiderotic changes. The iron stores will be overloaded, despite a persistance of the hypoferremia. In some patients with ulcerative colitis it might be suspected that there would be no response at all to iron therapy. In such cases, however, spontaneous improvement of the anemia may be expected when remission occurs. When it is assumed that rapid improvement of the anemia might benefit patients with severe symptoms, this can be accomplished by blood transfusions.

Summary

The cause of the anemia associated with chronic ulcerative colitis has been studied in 9 children with this disease. The iron metabolism has been investigated by means of the use of radioactive iron and determinations of the serum iron level and the concentration of the iron-transporting protein in the serum.

Most of the children with ulcerative colitis had a slight or moderate normochromic anemia with a low serum iron level. Despite the low serum iron level the concentration of the iron-transporting protein was normal or subnormal. The patients showed high absorption of a test dose of labelled iron given by mouth, but there was a slow rate of utilization of the iron absorbed.

On the basis of our results, it might be concluded that the cause of the anemia complicating ulcerative colitis is not only iron deficiency but also a disturbance in iron metabolism, or erythropoiesis, of the same type as seen in infections, and some chronic systemic diseases. The therapy of the anemia has been discussed with regard to this conclusion.

L'étiologie de l'anémie chez les enfants atteints de colite ulcéreuse chronique.

L'étiologie de l'anémie a été recherchée chez neuf enfants atteints de colite ulcéreuse chronique. Le métabolisme du fer a été étudié par l'emploi de fer radioactif, de la détermination du taux de fer sérique et de la concentration dans le sérum de la protéine transportant le fer. La plupart des enfants atteints de colite ulcéreuse présentaient une anémie normochrome légère ou modérée avec une concentration de fer sérique abaissée. La concentration de la protéine transportant le fer était normale ou sous-normale malgré une concentration de fer sérique diminuée. Les patients présentaient une absorption élevée d'une dose déterminée de fer marqué donnée par voie buccale, mais l'utilisation du fer absorbé était ralentie. Se basant sur nos résultats on pourrait conclure que la cause de l'anémie comme complication d'une colite ulcéreuse n'est pas uniquement une déficience en fer mais aussi un trouble du métabolisme du fer ou de l'érythropoièse tel que l'on observe dans les infections ou certaines maladies chroniques généralisées. Le traitement de l'anémie a été discuté en se raportant à cette conclusion.

Die Ursache der Anämie bei chronischer Colitis ulcerosa.

Verf. untersuchte an Hand von 9 Fällen die Ursachen, welche bei der chronischen Colitis ulcerosa zur Anämie führen. Mit Hilfe von radioaktivem Eisen wurde der Eisenumsatz verfolgt und Bestimmungen des Serumeisenspiegels und der Konzentration der eisenbindenden Proteine im Serum vorgenommen. Die meisten der Kinder mit Colitis ulcerosa hatten eine leichte bis mässige, normochrome Anämie mit einem neidrigen Serumeisenspiegel. Ungeachtet dieses niedrigen Serumeisenspiegels war die Konzentration der eisen-transportierenden Proteine normal oder subnormal. Die Patienten zeigten eine zufriedenstellende Resorption einer Testdosis markierten Eisens, welches peroral gegeben wurde, aber das absorbierte Eisen wurde nur langsam weiter verarbeitet. Auf Grund dieser Resultate kann der Schluss gezogen werden, dass die Anämie, welche bei Colitis ulcerosa auftritt, nicht allein durch ein Eisendefizit bedingt ist, sondern auch durch eine Störung im Eisenumsatz oder in der Erythropoese, analog denjenigen Anämien, welche nach Infektionen und bei einigen chronischen Systemerkrankungen beobachtet werden. Unter Berücksichtigung dieser Schlussfolgerungen diskutiert Verf. schliesslich die Therapie dieser Anämie.

La causa de la anemia asociada a la colitis ulcerosa crónica.

La causa de la anemia asociada a la colitis ulcerosa crónica ha sido investigada por medio del uso de hierro radioactivo y determinaciones del nivel de hierro en el suero y de la concentración de proteína hierro-transportadora en el suero. La mayoría

de los niños con colitis ulcerosa tenían una ligera o moderada anemia normocrómica con un bajo nivel de hierro en el suero. A pesar del bajo nivel de hierro en el suero la concentración de la proteína hierro-transportadora fué normal o subnormal. Los pacientes mostraron alta absorción de una dosis test de hierro marcado dado por boca, pero hubo una lenta utilización del hierro absorbido. Sobre la base de nuestros resultados, podría concluirse que la causa de la anemia complicando la colitis ulcerosa no es solo la deficiencia de hierro sino también un disturbio en el metabolismo del hierro o de la eritropoiesis, del mismo tipo que se encuentra en las infecciones y en algunas enfermedades sistémicas crónicas. La terapía de la anemia ha sido discutida en base a estas conclusiones.

Acknowledgements

We wish to express our gratitude to Dr. R. Bonichsen for valuable advice with regard to the technique of measuring radioactive iron in biological material. We are also indepted to Miss Franzi Wagenberg for assistance with the determinations of the iron-binding capacity of serum.

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CASE REPORT

Adams-Stokes Syndrome Following Acute Hemorrhage in an Eight Year Old Girl

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The term Adams-Stokes syndrome is used in the case of syncope of cardial origin (WARBURG). It may be seen in the course of several diseases of which the atrioventricular block is by far the most important. It may also be seen during a sinoauricular block, a rather rare and often harmless phenomenon (THOMSEN, LANDTMAN).

A brief attack will cause general weakness, restlessness and fainting spells. Loss of consciousness, cyanosis and convulsions will usually result if the attack is prolonged. Recovery after a 2-minute attack is recorded, but most often the prognosis must be considered pessima, if the attack is not terminated in one minute.

Some of the recorded cases of Adams-Stokes syndrome seem to have developed in the course of infectious diseases (v. KISS, LEGROS & NASSHEUER) or as a later complication (CHRISTENSEN & DALGAARD, CHRISTOFFERSEN & VERMEHREN). Typical cases of Adams-Stokes syndrome on the basis of verified pericarditis (STERN) and chronic myocarditis (MEHLSEN & ESKELUND) have been recorded; SIEGEL saw one originating from a septal defect.

Electrocardiograms of such attacks are rare. It may therefore be of interest to present this case.

Case History

Our patient, an eight year old girl, had not previously suffered from rheumatic fever or diphtheria, and she had not had any cardio-pulmonary symptoms.

Present illness: For several days before admission the girl had had a cold and had been running a temperature of about 38°C. Two hours before admission the mother had noticed that the patient, while asleep, was bleeding from the right nostril. She was very pale and shortly afterwards she had severe hematemesis with several coagula. Because of the severe epistaxis the patient was brought to the Ear-Nose-Throat Clinic. Upon admission she was very faint, tired and complained of dizziness. Occasionally she fainted, and the pulse was very weak and variable. Due to this she was immediately admitted to the pediatric department.

Physical examination: The girl was very pale and too weak to sit up. The pulse rate varied between 100—40 per min., and the blood pressure varied from 80/40 mm to 120/100 mm Hg. During the first hour after admission she had five fainting spells lasting from 2 to 5 seconds; these started with increasing restlessness and a snoring respiration; the pulse was not detectable and heart beat could not be heard. The eyeballs were directed upwards and showed a vertical nystagmus. However, there were no convulsions.

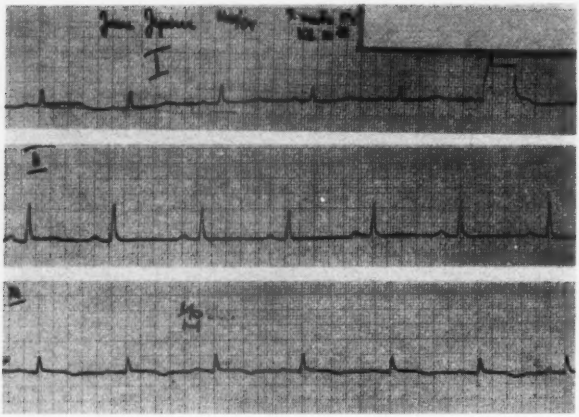

Fig. 1. ECG 2–3 minutes after a typical attack. Note isoelectric T_2 and negative T_3. Length of Q–T is within physiological limits (Q–T = $\frac{1}{8}$ R–R + 0.28 ± 0.05 sec.).

An electrocardiogram taken about 5 minutes after such an attack showed regular rhythms of 100/min. with T_2 isoelectric and T_3 negative. Q–T did not exceed physiological limits (Q–T = $\frac{1}{8}$ R–R + 0.28 ± 0.05 sec. (WARBURG, 1946). P–Q was normal (Fig. 1). Because of the frequent attacks the electrodes were left on the patient; the ECG was not writing, but only registering the heart beat. When it was apparent that the pulse rate was decreasing, the tracings were recorded. At that point the ECG showed a decrease of the heart frequency with the P–P intervals rising from 0.8 to 1.5 seconds. The patient became restless and groaned before losing consciousness. The ECG showed a 12 second cardiac arrest without any sign of cardiac activity (Fig. 2). This attack was also followed by a short period of slight but significant changes of the S–T, as those described above.

The patient had several light attacks similar to those described above during the first four hours in our department. Because of her uneventful past history we assumed a close connection between the large hemorrhage and acutely diminished blood volume and her unstable condition. She was therefore given an intravenous transfusion of her father's blood. From then on she improved rapidly and no longer had even the slightest fainting spells.

In order to be quite certain of recovery, more ECG's were taken immediately before (i.e. about half an hour after the last attack), during and after the transfusion. All these, together with some taken two weeks later, turned out to be quite normal (Fig. 3); only $QRST_3$ had changed its configuration without however being pathological.

Atropine, ephedrine and other drugs supposed to counteract Adams-Stokes syndrome were not given, because of the close relation between the blood-loss and the many attacks of syncope.

Discussion

It seems justifiable to assume that these attacks of Adams-Stokes syndrome type originated from the acute and rather large hemorrhage because (1) the patient was in good health until this event; (2) the tranfusion immediately relieved her unstable

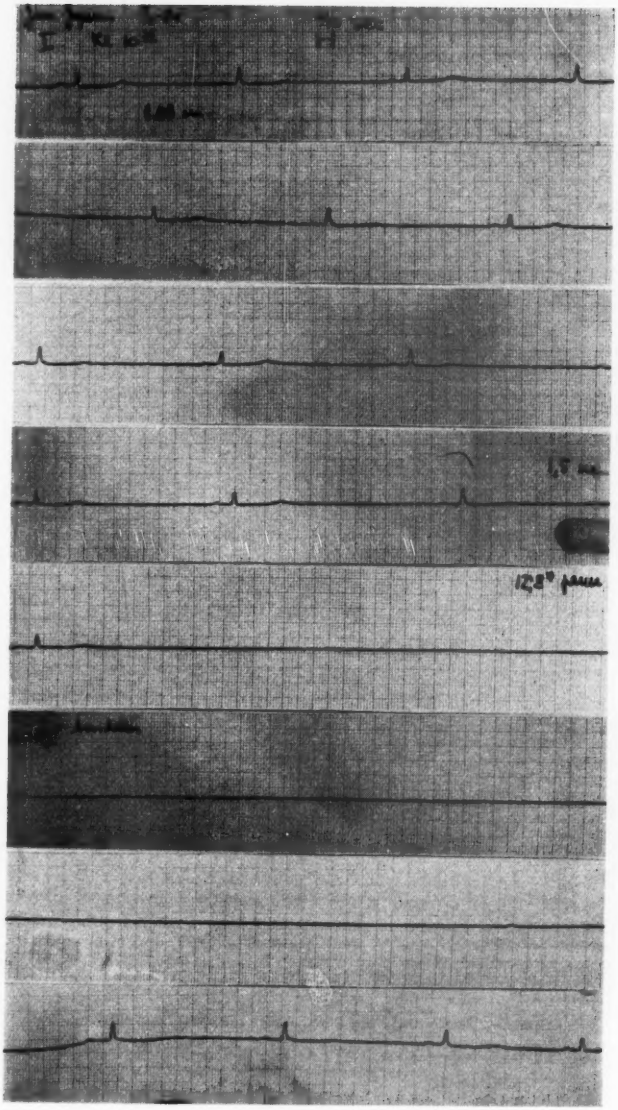

Fig. 2. ECG during a syncope. Note that intervals are increasing from 1.0–1.5 sec. before cardiac arrest.

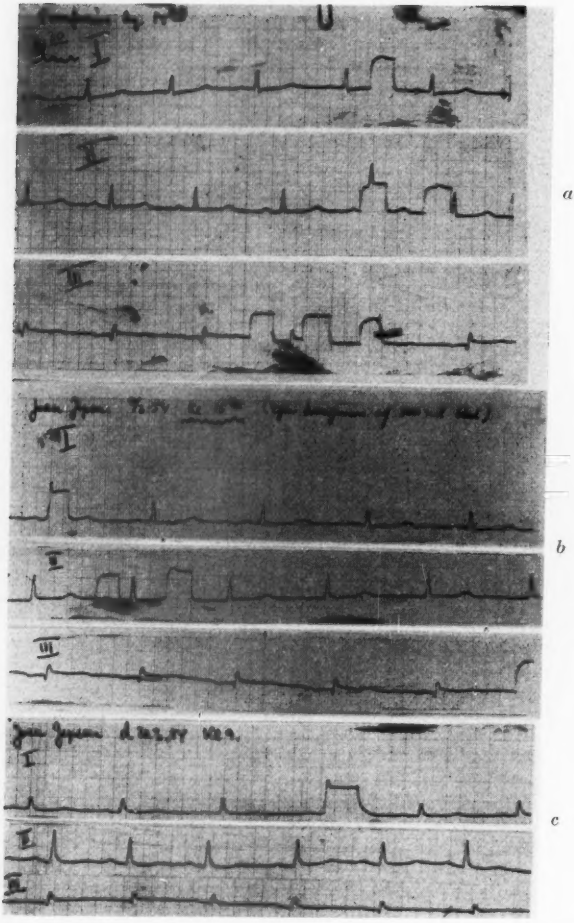

Fig. 3. ECG's immediately before and after transfusion (*a*, *b*) and two weeks later (*c*). They all show a normal pattern. Note that T_2 and T_3 are positive even before the transfusion (compare Fig. 1).

situation; and (3) no electrocardiographic sign of failing activity of the heart was found after the transfusion.

In connection with this case it must be kept in mind that the blood pressure in the coronary arteries varies according to the pressure in the aorta and that coronary failure is always detrimental to the activity of the heart muscle. In an acute and severe hemorrhage it may be difficult for the vascular system to adapt itself to the diminished blood volume; if it does not succeed, the function of the heart muscle will suffer.

In exsanguinated dogs it has been demonstrated (CRILE and DOLLEY) that the heart beat recommenced once the pressure in the aorta rose again. Later it has been shown clinically that quick intra-*cardial* or intra-*arterial* infusions may be extremely valuable in certain cases of imminent or actual cardiac arrest (DEVITT and WIGDEROW, ALEXANDER and HEWER). Intravenous infusions should be avoided, because the risk of pulmonary edema is too great.

In our case the heart muscle had not yet been sufficiently damaged as a result of the several attacks of hypotension; therefore the heart had no difficulty in transporting the increased volume offered to its right side.

Summary

A case of Adams-Stokes syndrome following acute hemorrhage in an eight year old girl, is reported. A cardiac arrest lasting 12 seconds was recorded electrocardiographically. Later ECG's did not show any pathological features. The attacks ceased after a single intravenous transfusion of blood. Several authors warn against intravenous infusions during imminent or actual cardiac arrest, as these may cause pulmonary edema. In such cases the intra-*arterial* route would be preferred.

Syndrome d'Adams-Stokes suite à une hémorragie aiguë chez une fillette de 8 ans.

Un arrêt du cœur pendant 12 secondes a été enregistré à l'électrocardiographe. Des électrocardiogrammes faits ultérieurement n'ont montré aucun signe pathologique. Les attaques ont cessé après une seule transfusion intraveineuse de sang. Plusieurs auteurs mettent en garde contre les infusions intraveineuses pendant des arrêts imminents ou existants du cœur, celles-ci pouvant occasionner de l'œdème pulmonaire. Dans tels cas la voie intra-artérielle serait préférable.

Adams-Stokes Syndrom nach einer akuten Blutung bei einem acht Jahre alten Mädchen.

Ein 12 Sekunden dauernder Herzstillstand wurde elektrocardiographisch registriert. Spätere Elektrocardiogramme zeigten keine pathologischen Veränderungen. Die Anfälle hörten nach einer einzigen intravenösen Bluttransfusion auf. Verschiedene Autoren warnen vor intravenösen Infusionen bei drohendem oder akutem Herzstillstand, da sie zu Lungenödem führen können. In solchen Fällen ist der intraarterielle Weg zu bevorzugen.

El síndrome de Adam-Stokes siguiente a una hemorragia aguda en una niña de 8 años.

Se registró electrocardiográficamente un paro cardíaco de 12 segundos. Los electrocardiogramas posteriores no mostraron ninguna alteración patológica. Los ataques cesaron después de una única transfusión intravenosa de sangre. Varios autores advierten contra las infusiones intravenosas durante paro cardíaco inminente o actual, pues pueden causar edema pulmonar. En tales casos debería preferirse la vía intraarterial.

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PROGRESS IN PEDIATRICS

Hospitalization Symptoms in Children

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The development of a child's personality is wholly dependent on a close, warm and continuous contact in early childhood with one single mother figure, whether the biologic mother or a permanent mother substitute. It is also very important that this contact answers to the child's emotional demands. In this connection, the term mother substitute signifies an adult, for instance a father, a foster mother, or a nurse. This is particularly desirable during the first three years when the child, so to speak, senses its way through life, but has not yet learnt to talk, being unable to think logically and abstractly, or to plan ahead.

Before birth, the contact between mother and child is complete. The child is a part of the mother and entirely dependent on her vital functions. At parturition, this perfect contact is broken, but the child characteristically persists in its entire dependence on the mother, or mother figure. At first, the child is purely governed by impulse, living wholly according to the principle of desire. Broadly speaking, an infant has only one desire—food, through which it comes in contact with the maternal body and is subject to her tenderness. An infant has no conception of time and demands immediate satisfaction. When it is about two or three months old and has begun to focus its eyes on objects in its nearest surroundings, the first manifestation of a positive realization of contact is, under favourable circumstances, the smile. Towards the end of the second quarter, the infant gradually and with great effort succeeds in identifying its mother. Its dependence on her grows stronger and stronger until a maximum is reached at the age of eighteen to twenty-four months. The mother represents its entire world and the child is selfishly and intensely dependent on her and is most sensitive to any disappointments. At that age it is particularly important that the child is taken care of by one single mother figure, a change often causing behaviour disturbances. When the child reaches the age of two to three years, it gradually loses its need of a purely physical contact with the mother. However, it still wants to be near its mother continuously, for

security, protection and understanding. Also at this age, radical alterations or a change of environment may seriously harm the child. At the age of three, its facilities for contact increase, *inter alia*, in the ability to talk. The child now does not live only in the present, more and more relaxes its dependence on the parents, gets into contact with other people and tries to unite different and often conflicting desires and requirements. However, if this process of mental development is to run smoothly, the influence of a mental organizer is important, viz., that of the mother. Although the child, after three or four years of age, has still a marked emotional hunger and a considerable need of security, separation from the mother, for a varying length of time from this age upwards, will entail a decreasing risk of major emotional disturbances, contrary to the stages in a child's development roughly outlined above.

Definitions

A manifestation of hospitalization symptoms will be defined by the present authors, in accordance with the Anglo-Saxon literature, as hospitalism, this term being conceived in the spirit of SPITZ's (38) definition: "a vitiated condition of the body due to long confinement in a hospital, or the morbid condition of the atmosphere of a hospital. The term has been increasingly preempted to specify the evil effect of institutional care on infants, placed in institutions from an early age, particularly from the psychiatric point of view."

Particularly since the last World War, hospitalism has been studied, *inter alia*, under WHO's direction, in children who have for varying periods during their first years of life been separated from their mother and retained in children's homes, hospitals, evacuation homes or other institutions. For a complete history, consult J. BOWLBY's well-known WHO report of 1951 (6), in which his own papers and those of other investigators are compiled. Another leading authority in this field is J. ROUDINESCO of Paris (31–34). The first Swedish description of mental impairment as the result of long periods in hospitals or children's homes was presented by KLACKENBERG 1946 (18). The hospitalization symptoms have been studied by various authors (1, 6, 14, 18, 25, 33–34, 36, 38, 39), in general by three different methods: *direct* studies of children at institutions, hospitals or foster homes, *retrospective* studies of youth and adults showing signs of mental illness, and *follow-up* studies of groups of children treated at institutions or hospitals. These investigations throughout disclosed the fact that a child under such conditions runs a great risk of being inhibited emotionally, physically, intellectually, as well as socially. What happens in those circumstances is that *one* form of maternal deprivation is established, a term used by BOWL-

BY, among others, to denote a disturbance in the natural mother-child contact. The circumstances under which maternal deprivation occurs can be roughly divided into two groups, as follows: *partial deprivation*, when the child lives together with the mother (or permanent mother substitute) but is not treated with sufficient affection, and *complete deprivation* in case where the child has been admitted, for medical or social reasons, to a children's home or hospital where a mother substitute who might have satisfied its needs of personal care and security is lacking. In the present paper, a brief account will be given of some of the observations and investigations made on the latter group.

Etiologic Aspects

The principal factor in the origination of hospitalization symptoms is the *child's age*. In the introduction the age of three to four years was mentioned as being particularly vulnerable. However, several authors have reported that children of seven or eight years of age can also take harm from a lack of maternal care (6, 9). This upper limit on the whole meets with agreement in the literature, but opinions differ more concerning the lower limit at which any harm is conceivable. BOWLBY (6) and ANNA FREUD contend that "separations and deprivations in the first six months of life were less important for the child's welfare than later ones". BOWLBY adds that experience has shown that when children, who have entirely lacked a mother figure up to the age of one year, are adopted at that age, the prospects of a sound development are favourable. Finally, it is characteristic of the younger age-groups that those who earlier had a good contact with the mother react strongly to separation, while, in the older group of five to eight years of age, children who have had a happy childhood tolerate separation better owing to their greater emotional maturity.

As regards the *duration of the separation* from the mother after which mental impairment is to be feared, BURLINGHAM & FREUD (6, p. 24) point out (on the basis of studies over several years of children in evacuation homes during the last war) that children between $1^1/_2$–$2^1/_2$ years cannot be separated for more than a day without a regression in their behaviour. As a rule, the children recover from a lack of mothering for less than three months in the first two or three years of life, but deprivation for more than five or six months entails a serious risk of irreversible injury, in spite of satisfactory treatment from a purely technical point of view (6).

The *quality* of the mother-child relationship before and after the separation as well as the *cause* of the latter are of course factors of great significance to which we shall return later in another connection. An additional factor of importance is the child's *experiences* during hospitalization, and

of the mother substitute, if any. Several authors emphasize that the more complete the deprivation during the first years of life, the more isolated and asocial the child; the more the separation takes place with feelings mixed with satisfaction, the more ambivalent and antisocial the child (6).

Also *hereditary* factors have been considered to contribute to the occasionally enduring effects of hospitalization. ORGEL, BROWN (6, p. 41) and BODMAN *et al.* (5) assert, on the basis of their own analyses, that constitutional and hereditary factors seem to be as important as environmental factors in social adjustment. However, a number of inverstigatos, headed by SPITZ (38, 1945), ROUDINESCO & APPELL (33, 1950), and SIMONSEN (36, 1947), examined children manifesting symptoms of hospitalism, comparing them with control groups of healthy children with a similar social and hereditary background and excluding as far as possible the influence of congenital factors. They inferred that it is hardly likely that hereditary factors bear the main responsibility for the retardation effects manifested in hospitalism. Since, according to WALLGREN (46), a congenital neurolabile constitution is often observed in children with the abnormal mode of reaction to different trials appertaining to it, definitely hereditary factors can therefore partly be the cause of hospitalization reactions.

Symptomatology

During the *first period of separation* most children at the age of one to three years are subject to a series of undifferentiated and frequently instinctive reactions, expressive of their deep mourning for the loss of their mother. According to BOWLBY (8) these cases are roughly divided into three consecutive stages, viz. (1) *protest*, (2) *despair* and (3) *denial*. Here an attempt will be made to exemplify them.

1) When the child has been left alone, it screams loudly, tears its clothes and tries to do everything in its small power to attract the mother's attention. It is seized by a violent alarm when she does not come and feels confused in its new surroundings, listens tensely to every sound which may prove to be the longed-for mother. Some children calm down temporarily when anybody enters the room, but resume their crying as soon as they are left alone again, while the children who can talk try to put their despair into words. Some few children fail to react in this way, at once taking an active part in all that happens around them. They are gay and amiable towards the grown-ups and seem independent. In actual fact, they represent an abnormal, pathological behaviour, because of early unhappy experiences of the mother or substitute (8).

2) After this initial stage, which may last from hours to days, most children pass into a state of despair. Their screaming becomes more monotonous and intermittent, their crying grows less vehement. Their behaviour is quieter, they become slow and listless. When left alone, they sit still without touching their toys, having a stereotype, tense expression. They look about them with despair. When a grown-up enters the room, they follow her with their eyes with an unchanging expression. However, when the grown-up approaches them, this attitude changes, and then children react differently. Some do not show any interest whatever in the grown-up and are quite passive when dressed and fed. They display neither joy nor annoyance at being lifted up. Far more commonly, children will repel the grown-up by screaming and kicking. Toys offered them are thrown on the floor. They refuse to take food and keep their mouth obstinately shut. Yet another mode of reaction is when a child discloses an intense longing after purely physical contact with a grown-up. Here, for instance, the child wishes to be carried and clings to anybody. Often the mere presence of a grown-up in the room is enough for the child to feel calmer. — Also a series of regressive and primitive symptoms are described, such as the loss of ability to walk, although the child may have been confined to bed for a short period of time only. Or, it loses bowel and bladder control, resumes thumb-sucking, masturbates, sits rocking and shows jactation—broadly speaking, returns to babyhood. Some ordinary psychosomatic signs of anxiety are: a frequent desire to urinate, diarrhea and vomiting. As regards the twenty children at the age of twelve to seventeen months examined by Roudinesco *et al.* (32), all disclosed a loss of weight during the fifteen days of observation. Nightmares and night fear sometimes occur, resulting in disturbed sleep. Often some beloved object with a home-like smell (e.g., the favourite toy, a rag or mummy's socks) is seen to divert the child's anxiety during its stay in the strange surroundings. For example: Hans-Erik, five years old, refuses to take off his cap during the first week at hospital other than at night, and is always trailing an old rag dog along with him.

3) The third stage, denial, which occurs in most children after about two weeks' separation from home, is characterized by the fact that the child no longer so openly reveals the need of satisfying its emotional desire. It begins to take more of an interest in its surroundings, which is often misinterpreted as a sign of recovery. If the child does not obtain a lasting mother substitute, or has bad experience of frequent changes of nurse, it no longer dares take the risk of bestowing its affection or dependence on anybody. It becomes increasingly egotistic, is fearless and has but little need of social contact, does not make any deep and lasting emotional con-

nections, appraising others only by their gratification of its material wants. The child no longer discloses any selective urge for contact, viewing all grown-ups in the same light. These children are often gay and amiable. Some of them show a defective power of concentration and are hyperactive. This relatively calm and, apparently, well-adapted exterior often conceals strong aggressions which are, sometimes, manifested by unmotivated, violent fighting or pronounced destructive tendencies in handling toys.

A film taken by ROBERTSON & BOWLBY (29) clearly shows an objective registration of a child's behaviour during its stay at hospital for eight days. It reproduces the reactions before and after an operation for inguinal hernia of the girl Laura, aged two and a half. Several of the symptoms described in the two first-mentioned stages are here clearly manifested. In addition, her *behaviour at the parent's visits* is typical of the majority of children at an age of one to three years under similar conditions. At first they often scream or refuse to take any notice of the parents—this being an expression of the conflict between the child's strong yearning for the mother above all, and its profound disappointment at having been forsaken by her. However, after a while their negativism decreases and is replaced by a softer attitude. These emotional manifestations at sporadic visits by the parents, as a rule, become less intense after a few weeks, and the child reacts less and less.

The symptoms described above, manifested normally by a child of 1–3 years of age at separation from its mother, become less marked when the child learns to talk and can express its anxiety in words. The facilities thus obtained for communicating with its surroundings reduce the risk of permanent injury.

In this connection, it should be pointed out that in judging hospitalization reactions, due regard must be paid to whether the child is ill or not. This has not, in our opinion, been sufficiently clearly stated in the works by BOWLBY and ROUNDINESCO, whose materials largely comprise hospital children (ANNA FREUD 13, 1952). On the other hand, PRUGH *et al.* (28), in their investigations in 1953 of 100 sick children, stressed the difficulty of distinguishing between reactions due to separation from the mother and those elicited by the illness as such. These variables emphasize one another and strengthen the effect. Of particular interest is ANNA FREUD's description of the most common modes of reaction observed in a sick child obtaining good treatment at home, which on the whole conform to the hospitalization reactions previously mentioned. On the basis of the analyses of cases of this kind, she emphasizes the fact that, in recent investigations concerning the effect of hospitalization on small children, attention has been directed only to the harm occasioned by separation from the mother and the home,

and that in cases submitted to hospital treatment nothing has been said regarding the child's reaction to the disease itself or to the pain. In future further analysis of the risks of the hospitalization of children, viewpoints like those of the above author will have to be taken into consideration. A healthy child who is admitted to a children's home, or some similar institution, can divert some of its emotions by running about, whereas the sick child is often enough not only confined to bed but may also harbour a subjective feeling of illness. Further, the latter children are often subjected to painful examinations and surgical interventions. To a small child, even a minor operation is a great and terrifying event, as there is no proportional connection between the objective and the subjective conception of pain. Irrespective of the extent of the surgical intervention, it gives rise to emotional disturbances, even when the anxiety of separation is not involved (12). Other procedures that meet with strong reaction from some children are, *inter alia*, injections, the taking of the temperature per rectum and manipulations in the genital region.

Finally, an example will be given of a hospitalization reaction in a boy of one year of age, Jan-Erik. Diagnosis: Anorexia nervosa (hospitalism). The only child of middle-aged parents. Normal delivery. Birth weight 3,900 g. Breast-fed for 9 months. He was admitted owing to slow increase in weight due to a refusal to eat. After a few days at the somatic department, he was transferred to that of child psychiatry. In the first few days, Jan is silent and pitiable, and "gives the same impression as a grown-up, inhibited and depressive person". He shows no spontaneous joy, and when tickled smiles rather to oblige. His whole body seems hypotonic and he walks less well than before. His toys lie untouched. The mother is then told to come and visit him as often as possible. She comes daily and plays with him, takes him in her lap but does not feed him. Already after 4–5 days, the boy changes, becomes more active, more spontaneously happy and prattles. To begin with he does not recognize his mother, but gradually shows pleasure at her arrival, though not reacting on her departure. "He has never been so starved for his mother that he has been unable to tear himself from her." At his discharge after a little more than a month he had improved.

As regards the behaviour of children just *after a brief period of hospitalization*, several direct investigations have been performed in recent years (6, 10, 15, 16, 21, 23, 25, 28). ROSENBLUTH *et al.* (30) reports, among others, two important behaviour patterns shown by children at the age of five to six years on their return home. First an emotional coldness. The child does not take any notice of the mother or is stiff, unmoved or even hostile. After a few hours or days, this condition as a rule suddenly changes, being fol-

lowed by an intense and demanding dependence on the mother, with violent outbursts of emotion and tears, expressive of the fear of again losing her. The child often refuses to lie alone at night, is jealous when the mother interests herself in other children and is liable to explosive fits of anger when the mother disappoints it. It constantly keeps an eye on her doings and always wants to be close to her. This increased mother fixation is so common as to be interpretable as a normal consequence of separation (23). Even though the child's conduct at the home-coming is taken wisely by the parents, it may persist for several weeks or months. A faulty treatment may cause enduring disturbances in the child's relation to the rest of the family and gradually diminish its possibilities of coming into contact also with other people.

Some investigations on children subjected to minor surgical interventions illustrate fairly well these reactions after the home-coming. ECKENHOFF (10) examined 612 children of an age of from to 2 to 11 years after ear, nose and throat operations. Two months later, he found that seventeen per cent of the children had been subjected to personality changes that might be attributed to the hospitalization and operation. JACKSON *et al.* (15, 16) examined 140 tonsillectomized children, aged 3–8 years, both immediately and three months after the intervention. The examinations immediately afterwards were, on the whole, disregarded as the children at the time suffered from physical troubles (pain in the throat, etc). Three months later, some of the children (9 per cent) disclosed changes in their conduct which were considered pathognomonic of emotional trauma, viz., eating disturbances in the form of refusal or squeamishness, increased dependence on the mother, a hostile attitude to the parents, difficulty in putting the children to bed owing to recollections of the anaesthesia, often nightmares and, finally, sometimes regressions to earlier stages of development. As no penetrating psychologic examination could be effectuated, these observations only show that some children gave vent to conscious or unconscious feelings three months after the operation. By means of detailed interviews, a conception was obtained of the child's previous behaviour and mental status, showing that an earlier emotional trauma predisposed the child to a stronger reaction after the intervention in question. These two investigations confirm the observations made by LEVY (21) after tonsillectomy in children.

Persistent marked symptoms of hospitalism after the discharge are illustrated by the following case, concerning Birgitta, aged $3^1/_2$ years. Diagnosis: Neurasthenia (aversion to the pot). Normal delivery, birth weight and development without remark. The girl has never before been to a hospital or been separated from her parents for any particular length of time. The

is admitted to the somatic department owing to her fear of the pot, which is due to a fissure incurred after habitual constipation. She is "dethroned" by a sister, 4 months old. During her stay at the hospital she shows hospitalization symptoms; for instance, in the first week she insists all the time on being taken home, and reckons the time like this: "now I shall sleep twice, then mum and dad come back". A dirty painting rag from home is her means of diverting her anxiety. After two weeks, Birgitta is discharged. At home she is apathetic, cries almost all the time, cannot dress herself, cannot fasten her buttons. She begins to suck a teat. Her previously good sleep is now disturbed by terrifying dreams, mostly about her stay at the hospital where, in particular, the X-ray examinations seem to have left deep traces. Birgitta all the time thinks she has to go back to the hospital, until one day her mother after a week suggests that they send a cake to the nurses at the department. Now the girl realizes that she is home for good and not merely "on pretence". Her behaviour changes almost on an instant, she begins to eat with an appetite, dresses herself, etc. She often plays at hospital, distributes trays and lets her doll undergo an X-ray examination in a very illusory way. As regards her original troubles, she had only had one spontaneous evacuation in the past weeks but now, according to her mother, has satisfactory evacuations each night.

The *symptoms during and after prolonged hospitalization* are described principally on the basis of direct studies, but also on retrospective studies. A few concordant conclusions have been drawn: the ability to talk is particularly affected, partly owing to the fact that institutional children get so little training to talk as compared with family children. Next comes social adaptivity. The neuromuscular apparatus is the least affected, including the gait and the development of a right hand dominance. The ability to express oneself is more inhibited than that of understanding the spoken word. The extent of these reactions is diminished when a substitute mother is available.

Several clinical reports, among them the nowadays classical works by Spitz (38, 1945; 39, 1946), Simonsen (36, 1947), and Roudinesco & Appell (33, 1950), all with corroborating control groups, establish with striking conformity that the development quotient falls the longer the separation.

An account is given by Fried & Mayer (14, 1948) regarding the inhibition of physical growth due to institutional treatment. He found, in children aged 6–13 years from children's homes, that 75–90 per cent of the newly arrived disclosed a measurable disturbance in growth. This was noted in 15–20 per cent of those who had been there for 6 months or more, in spite of the very best material care. This clearly illustrates the connection between socio-emotional disturbances and inhibited growth.

The emotionally indifferent state to which a child succumbs even after a relatively short stay at a hospital under impersonal care may, if prolonged for at least 3 and probably more than 6 months during the first three years of life (6), originate a callous and psychopathic personality. BOWLBY reports another two experiences which may each produce this: no possibility of entering into *any* contact with a mother figure during the first three years of life, as well as frequent changes of mother figure during that period. These conclusions are confirmed, among others, by six authors who, independently of one another, studied retrospectively juvenile criminals, observing the following traits which they all had in common (6): "superficial relationship: no real feeling—no capacity to care for people or to make true friends; an inaccessibility, exasperating to those trying to help; no emotional response to situations where it is normal—a curious lack of concern; deceit and evasion, often pointless; stealing; lack of concentration at school". These investigators all noticed in these young people an incapacity to form deep and enduring human contacts which was manifested already in childhood, due in actual fact to institutionalism or to frequent changes of foster mother.

As regards *therapy* in these severe forms of mental trauma after hospitalization, BENDER (3, 1947), LEVY (20, 1937), POWDERMAKER *et al.* (27, 1937), among others, state that in the majority of cases therapy is ineffective, mainly owing to the fact that the therapeutist is unable to establish any emotional contact with the patient, which is a *sine qua non* of a successful treatment. Other authors like JONSSON of Skå Edeby, Sweden (6, p. 51) and BETTELHEIM & SYLVESTER of Chicago (4, 1948) view this treatment more optimistically, finding the prognosis hopeful when the child is first subjected to a regression to earlier infantile stages and then developed along more normal lines. However, this treatment is both expensive and lengthy. Therefore, we should aim at preventing such injuries by resorting to prophylactic means.

Prophylaxis

Attention has been drawn by several leading pediatricians (BAKWIN, SPENCE, WALLGREN, and others) to the risks of emotional trauma in connection with a *child's retention at a hospital*, but there is still much that requires reform in this field.

The indications for admission should be made more rigorous, particularly with regard to children in the vulnerable age; children with trifling somatic affections should not be admitted as a matter of course. "As a doctor's experience increases, the fewer are the children he confines to hospitals" (SPENCE 37).

The suitable day for admission is when the child is in its best emotional state, but it should be postponed in the event of a death or other major change in the child's surroundings.

The attitude of the parents to the child's hospital visit is important. As their alarm and anxiety are often transmitted to the child, this should be explained to them. The child should be informed in a simple way of what is going to happen at the hospital and why. Also the new surroundings should be described and it should be informed that it will be left alone sometimes. Several pediatricians (BAKWIN 2, 1951, NORDLUND, 25, 1952, PRUGH 28, 1953, SPENCE 37, 1947, and SÖDERLING 41, 1954) report favourable conditions of after-treatment for children who obtained a mother contact during their stay at the hospital and, at the home-coming, these children less often disclosed nervous disturbances like those described above. In addition, a more confident and relaxed relation between family and hospital is established and the nurses get more time to devote themselves to the other children. The ideal is frequent parental visits, preferably every day. The need of enlightenment on this point is evident from SELANDER's (35, 1954) interviews of over 400 mothers whose children had been nursed at a children's hospital: not less than 9 per cent of them considered visits quite unnecessary, while only 4 per cent wanted to come daily. The visits should be made particularly at psychologic times, such as food-time, bed-time, and, above all, pre- and postoperatively, when the need for security is most pronounced (41). When the child is left at the hospital, the parents should be allowed to stay for a few hours until the child's sometimes panicky reactions to the new surroundings have been mitigated. SPENCE (37, 1947), and some others, has provided mothers with facilities for staying at the hospital to take an active part in nursing the child, throughout with good results. If, for various reasons, the mother is prevented from visiting her child, SÖDERLING (41, 1954) mentions that a milder transition from hospital to home is created by letting the mother stay at the hospital for a few days with her child before the discharge.

The newly admitted child should be given an immediate and intense contact with a mother substitute. The latter should preferably be the same throughout the hospitalization and is, next to the mother, the one best suited for psychologically preparing the child for each painful treatment, anaesthesia or operation, so that the child understands that it is being done for its own good and not as a punishment. Painful and frightening procedures, such as adenoidectomies, cosmetic operations and allergic tests, should if possible be postponed until after the age of 3–4 years. As regards the preoperative treatment, anaesthetization of the child is recommended by most doctors, before being taken to the operation room, thus avoiding

the unpleasant experience of passing through long corridors, seeing the instruments and the staff with their mouth masks. To prevent inhibition of the psycho-motorial development, attention should be paid to the child's talking, walking, toilet training etc., and, in the case of school children to their education. Finally, the role of a play nurse is emphasized, as she can reduce the child's sense of anxiety and abandonment by providing it with stimulating occupations and contacts.

ANNA FREUD (quot. 23) sums up the most important things to be made clear to a child in a hospital: "He is still very much loved. He is not being punished. He is getting better."

Lastly, a few words will be added regarding the *care of somatically healthy children* who have to be admitted to children's homes, or similar institutions, for various reasons. It is necessary to find a form of treatment suited to each individual and corresponding to his or her age and degree of development. Particularly in the case of the younger children, a continuity in their relation to the person taking care of them is of great importance. Family care in these ages is the best, affording as it does most chances of satisfying the need of affection and giving a firm basis for the development of personality. For children at the age of 8–9 years and more, most authors (BOWLBY 6 and CLOTHIER 9, among others) recommend institutional care, preferably in small groups of 8–10 children of different age and sex, living in separate houses with a matron and, if possible, also a housemaster as parental substitutes. However good the conditions in such institutions, this form of treatment must be considered as the last expedient when a child can no longer live in its own home. Even if the child is ill-fed and ill-sheltered, dirty and feeble, suffering on the whole material want, but the parents do not entirely repel it, it nevertheless feels secure in the knowledge that someone cares for it and provides for it, however poorly. As BOWLBY (6) says somewhat pointedly: "Bad homes are often better than good institutions." Alongside with the endeavour to create better institutions for children, efforts must be made to improve the home environment by consultation, financial aid, etc.

Research in the past decades has shown that deprivation during childhood may cause more or less permanent injury. By continued studies, better facilities are obtained for preventing them, as well as offering an insight into the central processes of personal development.

Summary

A survey is made of the literature on injuries due to the hospitalization of children. These injuries are also illustrated by a few cases of our own. Etiology, symptomatology and therapy in hospitalism are discussed. Different prophylactic measures are presented as essential for the care of children in hospitals as wells as in institutions.

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The Danish Pediatric Society

Meeting, September 11, 1954

Meyer A. Perlstein (Chicago): **On Cerebral Palsy.**

Meeting, October 6, 1954

Chr. Hansted: **Child with Feminine Hermaphroditism.**

Anne Heerup: **Boy Aged 10 Years Suffering from Dermatomyositis.**

Stiffness of the fingers of the right hand developed at the age of 4 years and has since extended gradually to all the extremities. X-ray of the skeletal system revealed calcified plates in the subcutaneous tissue of the right thigh. Muscle biopsy: myositis of periarteritis nodosa type. Skin biopsy: fibrosis and very slight inflammatory changes. — Objectively, the skin appears transparent and atrophic. The musculature is atrophic and the mobility reduced in several joints. The course of the disease in general was described. Occasionally, but not invariably, good results have been obtained with ACTH and cortisone therapy, and such treatment will now be attempted in this patient.

Carl Friderichsen: **Waterhouse-Friderichsen's Syndrome. Diagnosis and Therapy.**

An increasing number of cases of W.-F. S. have been reported in the literature, probably on account of the increased possibility of effective therapy. The suprarenal insufficiency shows a characteristic clinical picture with an intermittent and variable form of cyanosis. The term W.-F. S. should be retained in those cases in which the suprarenal glands are attacked and show haemorrhage, necrosis, thrombosis or degenerative changes. Treatment should be directed partly against the infection (sulpha preparations and penicillin) and partly against the suprarenal insufficiency (cortisone and saline). This treatment should be administered both in W.-F. S. and in all forms of meningococcal sepsis. In W.-F. S., cortisone has proved life-saving. The dosage of cortical hormone may be controlled by daily eosinophile counts.

Discussion: *P. Schierbeck:* Is it really worth while saving certain children from this dramatic disease which involves such extensive destruction of the suprarenal glands? — *F. Neukirch* was of the opinion that the term W.-F. S. must be restricted to those cases in which changes in the suprarenal glands can actually be demonstrated. Among 631 cases of meningitis in Blegdamshospitalet (Hospital for Infectious Diseases, Copenhagen), 89 autopsies were performed. Twenty-two of the patients who died suffered from meningococcal infections and 10 died within 24 hours. In 9 of them a pronounced condition of shock was present. Suprarenal haemorrhage could only be demonstrated in 2 out of these 9 cases and these were patients who were moribund

on admission. The speaker stressed the difficulty of establishing the diagnosis during life. It might be anticipated that these patients would later develop Addison's syndrome, but this has apparently not been observed. — *A. Rothe-Meyer* also emphasized the difficulty of establishing the diagnosis during life; but the differential diagnosis from meningococcal sepsis is perhaps not so important since the treatment is more or less the same. — *C. Friderichsen:* The suprarenal glands certainly appear to be grossly injured but this is mainly due to haemorrhage. The speaker was of the opinion that recovery may occur and also stressed the diagnostic value of the characteristic cyanosis.

Helga Laursen: **Interstitial Pneumonia in Infants, with Particular Regard to the Etiology.**

A material comprizing 3 definite and one clinically probable case of interstitial pneumonia was presented. Of these, 3 died and one recovered. The infants were treated with the anti-protozoal preparations atebrin and plasmochin; apparently with better effect than that obtained with the ordinary antibiotic preparations. In 2 cases in which autopsy was performed, pneumocystis carinii was demonstrated in smears stained with Giemsa's stain. The epidemiology was discussed as the last three cases occurred in the same department and with an interval of one month between the first and the last two cases. Subsequently, the speaker reviewed the available literature concerning the etiologic possibilities. The protozoon pneumocystis carinii is regarded as the most probable causal agent, partly on account of its frequent occurrence in infants suffering from interstitial pneumonia, partly because the life-cycle has been elucidated and, finally, on account of the apparent effect of atebrin-plasmochin therapy.

Discussion: *C. Friderichsen:* Although attention has been paid to the possible occurrence of the clinical picture of the disease, no cases of the condition other than those described by Walther have been observed in Sundby Hospital (Copenhagen). The speaker mentioned the possibility that some of the pulmonary infiltrates occurring in older children may possibly be of the same origin. — *P. Bræstrup* presented one case from the Copenhagen County Hospital (Amtssygehuset), Gentofte. — *Elin Fog:* Could it be possible that aspiration infection from the vagina is concerned which only causes disease in premature and debile infants? — *H. Gormsen:* On revision of the histological preparations from the lungs in the cases of interstitial plasma cell pneumonia which I published in 1950 (Acta Pædiat. *39:*291–314, 1950), I have observed configurations which correspond exactly to the protozoa (pneumocystis carinii) described e.g. by Vanek & Jirovec in 1952 and, for the first time in Denmark, by Dr. Laursen, and which are possibly the etiological factor in this particular form of pneumonia. These configurations were observed in the sections stained with Giemsa's stain and were less convincing in the preparations stained with haematoxylin-eosin. The reason why these organisms have not been observed previously by the now numerous authors who have investigated this type of pneumonia is undoubtedly that the organisms are clearly visible only in *smears* stained with Giemsa's stain, prepared from the cut surfaces of the lung tissue. Paediatricians should, therefore, draw the attention of the pathologists to this fact in autopsies of suspected cases of interstitial plasma cell pneumonia. The disease must still be said to be rare in Denmark. To my knowledge, only 6–7 cases have been observed in Copenhagen. The geographic distribution of the disease is very peculiar. It is particularly striking that the disease seems never to have been observed in Britain or in the U.S.A.

It would be interesting to investigate if the protozoa described occur in those countries where the disease seems non-existent. — *K. Biering-Sørensen:* Are the protozoa sensitive to antibiotics? — *Flamand-Christensen* regarded the protozoa as pathogenic. Atebrin appears to be effective against them while antibiotics are not.

Meeting, November 24, 1954

E. Thamdrup: **A Case of Arthrogryposis Multiplex Congenita.**

The condition is characterized by congenital, as a rule symmetrical, contractures of a varying number of joints together with hypoplasia or aplasia of the musculature. A male infant, aged 2 months, was demonstrated with contractures of all the joints of the extremities. Muscle biopsy from the right tibialis anterior revealed muscular atrophy, probably of myogenic nature. No familial predisposition to the condition was stated. Oligohydramnia was probably not present. The infant was delivered as a breech-footling presentation and a fracture of the left humerus occurred during the delivery; no other osseous changes were present. WR and reaction for toxoplasmosis: negative. Serum calcium, serum phosphorus, serum phosphatase and excretion of amino acids in the urine: normal values. Ophthalmoscopic examination: normal findings. The condition does not appear to be progressive. Passive movement has improved somewhat following manipulations. The infant is not thriving well but the mental development appears to be normal. The pathogenesis was discussed; this is probably not the same in all cases. Muscular atrophy, either spinal or myogenic, developing early in foetal life, is perhaps the primary factor in the majority of cases. The significance of oligohydramnia (inhibition of foetal movements by which the development of the apparatus for passive movement is compromised) is a theoretical but not convincing possibility in a number of cases. In some cases, a more extensive mesenchymatous dysplasia seems to be concerned, as in addition to changes in muscles, joint capsules, ligaments and articular cartilage, changes may be encountered in the subcutaneous tissue.

Discussion: *Sv. Brandt:* The term arthrogryposis indicates a congenital condition which probably has several causes. If the cause is a malignant condition such as muscular dystrophy or spinal muscular atrophy, the prognosis is poor; but if the cause is not such a neuromuscular degeneration, commenced in utero, but for example depends upon congenital hypoplasia of certain muscles, the prognosis is far more favourable. The condition is very frequent in our orthopaedic hospitals, and orthopaedically much can be done to reduce subsequent later crippling. This does not, however, hold true of such severe cases as that demonstrated by Dr. Thamdrup nor the one I described previously.

J. Vesterdal and B. Friis-Hansen: **A Report of the Electrolyte Symposium in Zürich, October 1954.**

No account submitted.

S. Erup Jensen and M. Schneidelbach: **The Efficacy of Certain Preparations of Pancreatic Enzymes in Fibrosis of the Pancreas.**

The efficacy of various preparations of pancreatic enzymes was investigated on a boy suffering from congenital cystic fibrosis of the pancreas; he was in good general condition and aged 2 years and 9 months at the conclusion of the investigation. The

maximal dose recommended by the manufacturers was administered regardless of the enzyme content determined *in vitro*. The preparations employed were Pancreatin (RMC) (10 ml of the granulate thrice daily), Pankreon tablets (Rhenania) (3 tablets thrice daily), and Zymopan tablets (MCO) (3 tablets thrice daily). Clinical, biochemical and balance investigations were carried out during three periods for each substance, the diet being the usual for a child of that age. Without therapy with pancreatic enzymes, the fat and protein resorptions were 52–64 per cent and 40–48 per cent respectively (normal = 90 per cent or over for both values). The stools showed negative trypsin reaction; they were bulky, formed, pale and with cheesy odour; the average daily amount was 143–172 g (normal for patient's age: 50–60 g). The child was irritable and whining. During the periods of medication with Pancreatin RMC, the fat and protein resorptions were 80–86 and 71–86 per cent respectively. The stools showed positive trypsin reaction; they were entirely normal as regards consistence, smell and colour and less bulky with an average daily weight of 64–113 g. The child's mood was far better and he was more amenable. During the periods of Pankreon therapy, the fat and protein resorptions were 70–84 and 64–74 per cent respectively. The stools showed positive trypsin reaction; they were more fat and evil smelling and bulkier with an average daily weight of 105–133 g. Mentally the child was as during the treatment with Pancreatin. During Zymopan administration, the fat and protein resorptions were 60–65 and 49–63 per cent respectively. The stools showed negative trypsin reaction; they were even more bulky, loose and evil smelling with an average daily weight of 120–150 g. During these periods, the child was irritable, unpleasant and contrary. The sugar tolerance test, the patient's weight, general somatic condition and abdominal circumference did not show any definite relation to the various preparations.

Discussion: *Chr. Hansted:* A similar investigation was carried out on 3 patients suffering from coeliac disease with administration of Pancreatin for approximately one month with preliminary and subsequent control periods of the same length. During the entire experimental period, these patients showed reduced fat resorption and this was not improved by Pancreatin. It appears in addition from the curve of fat excretion for one of the patients with coeliac disease, that in this particular case a period of slightly less than three weeks elapsed before the fat excretion attained a fairly constant level on transition from the diet normally consumed by the patient to a gluten-containing analysed diet with a lower fat content of 35 g daily. Two of the patients suffering from coeliac disease were further examined in view of the effect of gluten-containing diet upon the fat excretion and, in agreement with the findings of J. H. van de Kamer, H. A. Weijers, W. K. Dicke and several others it was demonstrated that the fat resorption is reduced by a gluten-containing diet. It was apparent from the curves presented that long periods of investigation such as those employed are necessary to achieve reliable results in patients suffering from coeliac disease, partly because the fat excretion in such patients may vary markedly from day to day and partly because the effects of dietary changes are frequently not noticeable until after a latent period of 2–3 weeks. — *B. Friis-Hansen:* Why are the preparations effective in fibrosis of the pancreas but not in coeliac disease? — *Chr. Hansted:* Fibrosis of the pancreas is a condition due to defective resorption while coeliac disease is probably due to more extensive impairment of the fat metabolism.

I. Boesen and Sv. Brandt: **Prolonged Post-epileptic Aphasia in a Child Suffering from Untreated Seizures, Interpreted as Febrile.**

A girl aged 8 years was admitted with pyrexia (39.8° C, or 103.6° F.), unconsciousness and seizures which lasted for a couple of hours. In the subsequent weeks, it was difficult to obtain contact with her and on neurological examination, central and expressive aphasia was revealed. Focal EEG changes on the left side were demonstrated; the arteriogram was normal (left carotid); slight to moderate enlargement of the lateral ventricles and strikingly abundant superficial air on the left side on air encephalography; but apart from the aphasia, no objective neurological deprivation symptoms were encountered. The aphasia persisted for nearly two months but diminished gradually during that interval after which severe dyslectic symptoms were demonstrable so that special dyslexia education became necessary. From the age of two years, the child had suffered from several short generalized seizures in connection with pyrexia. None of these had been followed by deprivation symptoms. This child had never received anti-convulsant therapy and the explanation of this is probably to be sought in the fact that "febrile convulsions" are regarded by many as a benign condition with a favourable prognosis. The case history is recorded as an example of the trauma which may be the outcome of a prolonged epileptic seizure, viz. injury of the brain cells which are not always of a reversible nature. We are ignorant of the factors which determine the duration of a seizure and we can do nothing to shorten a seizure other than attempt anti-convulsant therapy. A prolonged traumatizing seizure may just as easily be the first as one developing later in a series of seizures.

Discussion: *C. Friderichsen* was not of the opinion that anti-convulsant should be instituted following an isolated febrile convulsion; the age of the patient and the duration of the seizure, for example, should always be taken into consideration. A case such as that reported, viz., a child aged 8 years with a prolonged seizure, would, however, always cause further investigation. — *P. Plum:* In the Pediatric Department, Rigshospitalet, the present procedure is that EEG is recorded on infants under one year who have had severe seizures once or twice. If the infant be over one year, EEG is recorded after an isolated seizure, whether this be slight or severe. — *A. Rothe Meyer* was of the same opinion. He emphasized, however, that prolonged treatment with phenemal (phenylethylbarbituric acid) is entirely without side-effects in young children as opposed to what holds true later in life. — *Sv. Brandt* felt, after the discussion, justified in drawing the following conclusion: There is unanimity that a child such as the one concerned here, ought to have been treated as an epileptic after the first seizures, perhaps already after the second seizure, while, on the other hand, numerous children develop an isolated seizure in connection with a pyrexial condition without ever having seizures later that expectancy is permissible as long as only one seizure has occurred. As opposed to Dr. Friderichsen and others, the speaker was not of the opinion that "the epilepsy bogey", with our present conception of this condition, is so terrifying for parents that, to avoid arousing suspicion of epilepsy, anti-convulsant therapy should be omitted in a child who for example has had two pyrexial convulsions, *although* normal EEG has been found, *although* the relatives are free from epilepsy, and *although* the two first seizures were benign, of short duration and without suggesting a focal lesion. On the contrary, according to the speaker's experience, the parents are so afraid of the recurrence of seizures

that they are comforted if suitable anti-convulsant therapy is administered. Epilepsy in children, from a statistical viewpoint, has a favourable prognosis. The parents should be told this. But the parents will want to know the prognosis for their child in particular and are not completely comforted by the fact that the risk of epilepsy following febrile convulsions is only 4–5 per cent.

Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, Oct. 15, 1954

B. Jonsson and U. Rudhe: **Primary pulmonary hypertension.**

Primary pulmonary hypertension is a rare disease of unknown genesis. Anatomically there are lesions in the small arteries of the pulmonary circulation with intimal swelling and narrowing of the lumina. Thrombosis increases the obstruction and further retards circulation in the lungs. Four cases were described with consideration of symptoms, physical findings, electrocardiography, roentgen changes, electrokymography, cardiac catheterization and angiocardiography. In order to establish the diagnosis, other causes of pulmonary hypertension must be excluded. A ventricular septal defect with high resistance in the pulmonary circulation need not produce any significant shunt and therefore cannot be excluded even by means of cardiac catheterization. Only the angiocardiography, with rapid injection of the contrast medium directly in the right ventricle, makes the diagnosis possible. In two of the cases the catheter passed an open foramen ovale and it was possible to demonstrate the characteristic pressure conditions with hypertension in the pulmonary artery, low pressure but atypical form of PCV, high pressure in PCA, and normal pressure in the pulmonary veins.

I. Engström, P. Karlberg and S. Kraepelien: **Studies of the pulmonary function in older children, especially asthmatic children.**

The technique of determining the vital capacity and the functional residual capacity was described. McMichael's method (closed system with helium as test gas and continuous oxygen supply) was modified somewhat in order to be used in children. The technical error in single determinations was found to be $\pm$ 6.3 per cent of the value, statistically determined from the difference of 65 double determinations. A group of 35 healthy children, aged 6–14, and a similar group of asthmatic children of the same ages without asthma at the examination have thus far been studied. The different pulmonary volumes showed good correlation to the body size of healthy children. Asthmatic children showed, in comparison with healthy children, an increased residual value and an increased functional residual capacity, positively correlated to the severity of the asthma. This was especially evident in the ratio-residual volume to total capacity and functional residual capacity to total capacity. Examples of the usefulness of these pulmonary function tests in evaluating the effect of treatment of the acute stage of asthma in children were demonstrated.

P. Karlberg and C. Berglund: **Respiration in the newborn.**

J. Lind and C. Wegelius: **Roentgenological studies of the respiration in newborn.**

The value of roentgen cinematography in the diagnosis and detailed analysis of the rapid dynamic action in the organism, for example the work of the heart, is evident. By the introduction of the image amplification system in cinematography a film with much smaller granules and with clearer details has greatly increased the quality of the pictures. Because the necessary dose of primary roentgen-rays for each picture can be diminished to a few per cent of the previous values, the total X-ray dose even with a very high frequency of the exposure over long periods can be kept below the risk limit. By roentgen cinematographic exposure in the angiocardiography of an infant with 32 pictures per second during 50 seconds or a total of 1600 pictures, the "r" dose in the air was found to be only 5 "r", which must be regarded as a very safe value. By means of this new technique the authors are engaged in a study of newborns in order to examine the dynamics of the first neonatal respirations and the changes in circulation at birth.

Discussion: *E. Mannheimer.* What are the advantages of this rapid microcinematography? Can it be of any additional value as compared with roentgenological methods used with pictures up to ten per second and in which the examinations are limited to a study of the individual pictures? — *Lind:* In order to get at total record of a very rapid dynamic course, as in the case of initial respiration, one has to work with markedly higher exposure frequencies than have been used until now and by which it is possible to follow and to evaluate correctly the process. Solely by a combined mode of action, in which the individual pictures are studied and in addition the film is turned, it is possible to get a more satisfactory evaluation. — *Vahlquist:* Is it possible that the quality of the pictures permits a more detailed diagnosis of atelectasis in the lungs of the newborn infant? Cases are well known in which roentgen pictures taken just before death show clear pulmonary fields, while at post mortem atelectic parts of the lungs have been found. — *Lind:* So far the described technique gives less sharpness and also less contrast than ordinary roentgen pictures. It is possible to expose individual pictures on a fine-grain film which is practically of the same value as an ordinary roentgen film. In cinematography one must, on the other hand, use a coarser grained film that gives somewhat less sharpness in the individual pictures.

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BOOK REVIEWS

Samuel Livingstone: **The Diagnosis and Treatment of Convulsive Disorders in Children.**

Charles C. Thomas, Springfield, Ill., U.S.A., 1954. 300 pages.

Dr. Livingstone is an assistant professor at Johns Hopkins Medical School and head of the Johns Hopkins Hospital for Epileptic Children. His experience is based upon a series of 4158 children. This is a rather well written text-book on epilepsy in children for general practitioners. The content is somewhat strongly schematized which may correspond to its didactic purpose. A short chapter is devoted to cranial radiology. The reviewer cannot agree with the author that pneumoencephalography can be done by anyone capable of performing a lumbal puncture. The EEG chapter is very short and comprehensive and shows some typical cases of easily differentiated forms of epilepsy. The therapy of the various types of epilepsy is excellently dealt with, showing the vast experience of the author.

M. d'Avignon

W. Penfield and *H. Jaspar:* **Epilepsy and the Functional Anatomy of the Human Brain.**

Little, Brown & Co., Boston, 1954, 896 pages.

This beautiful volume is the result of 15 years' collaboration between the authors. Penfield is one of the best known neurosurgeons, and Jaspar one of the leading neurophysiologists. The conception of the Montreal school of "Centerencephalon" is presented. Epilepsy is devided into two groups: centerencephal and focalcortical types. In the latter group an EEG-focus is demonstrable. The probable cause of seizures in children 0–2 years of age is delivery trauma, congenital disease or heredo-degenerative diseases. If the seizures start at 2–10 years, the cause may be birth trauma, thrombosis or a centerencephalic anomaly. A special chapter is devoted to functional localization in the cerebral cortex. The book can be recommended as perhaps the best one that has been published on epilepsy.

M. d'Avignon